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REACTION SCHEME 2

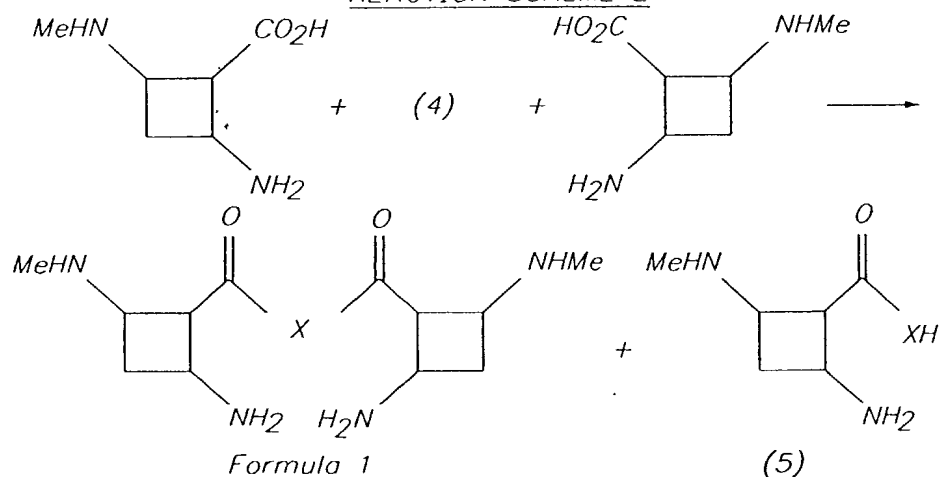


FIG. 1

REACTION SCHEME 3

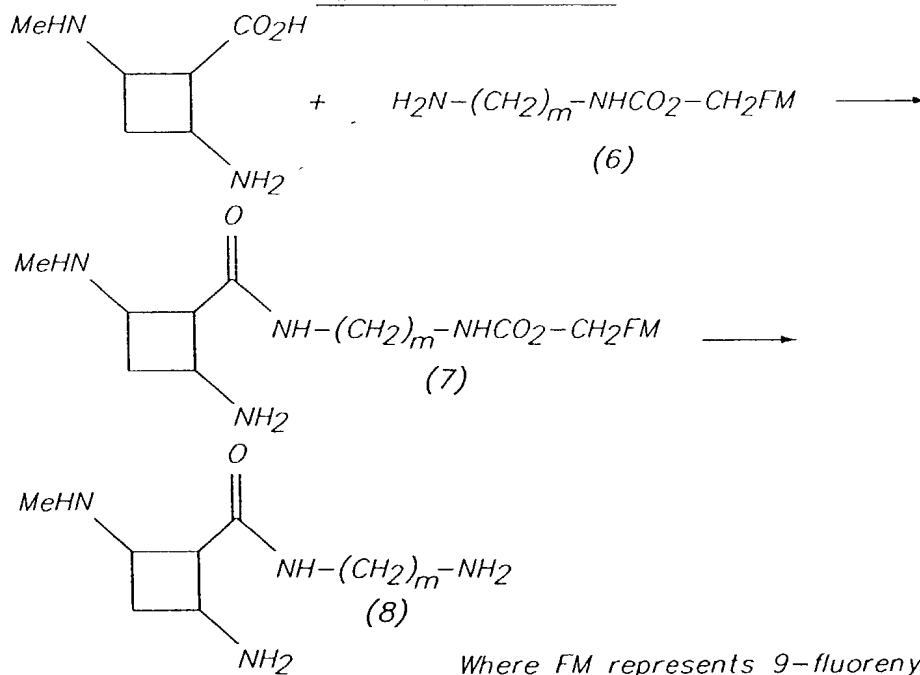
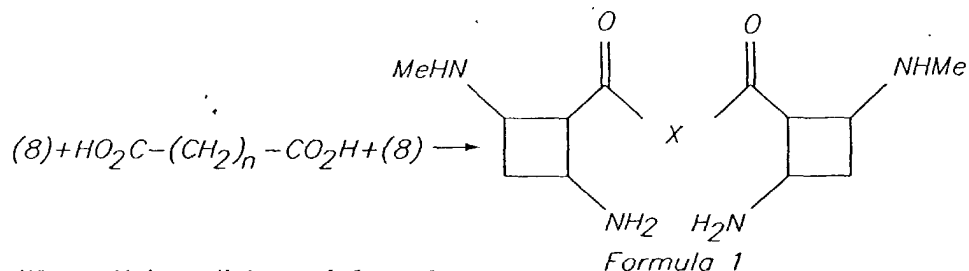


FIG. 2

Where FM represents 9-fluorenyl.,
and m is an integer of 1-20

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REACTION SCHEME 4

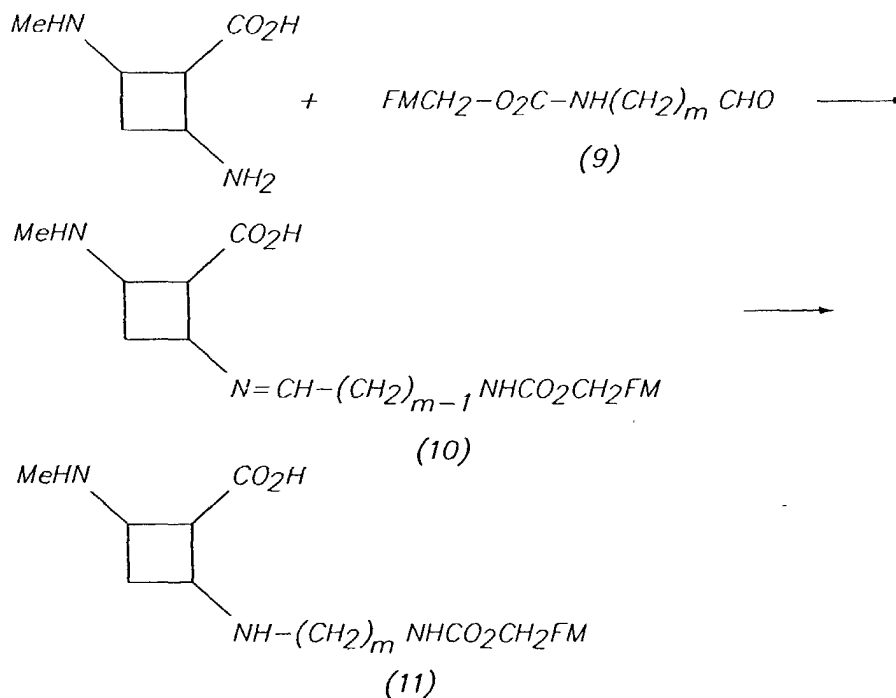


Where X is a linker of formula:

$-\text{NH}-(\text{CH}_2)_m\text{NHC(O)}(\text{CH}_2)_n\text{C(O)}\text{NH}(\text{CH}_2)_m-\text{NH}-$
 in which m and n are independently integers of 1-20

FIG. 3

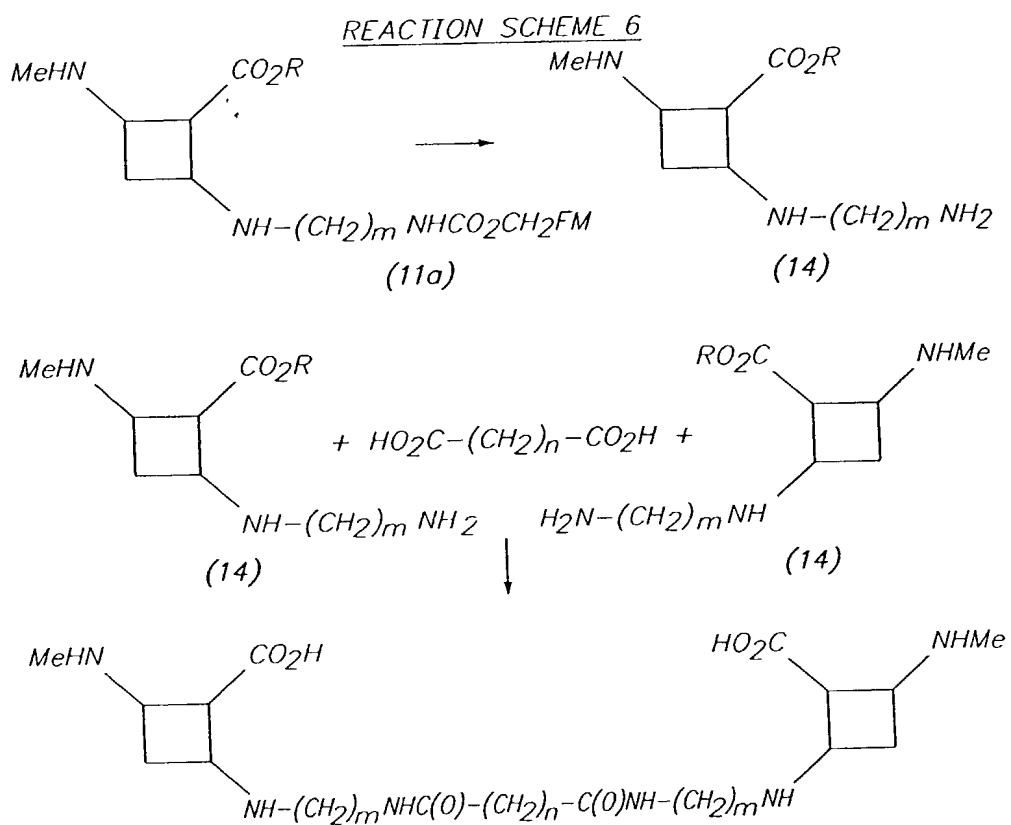
REACTION SCHEME 5



in which m is an integer of 1-20, and FM is 9-fluorenyl

FIG. 4

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where R is a protecting group, such as an ester, m and n are as defined above, and FM is 9-fluorenyl

FIG. 5

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REACTION SCHEME 7

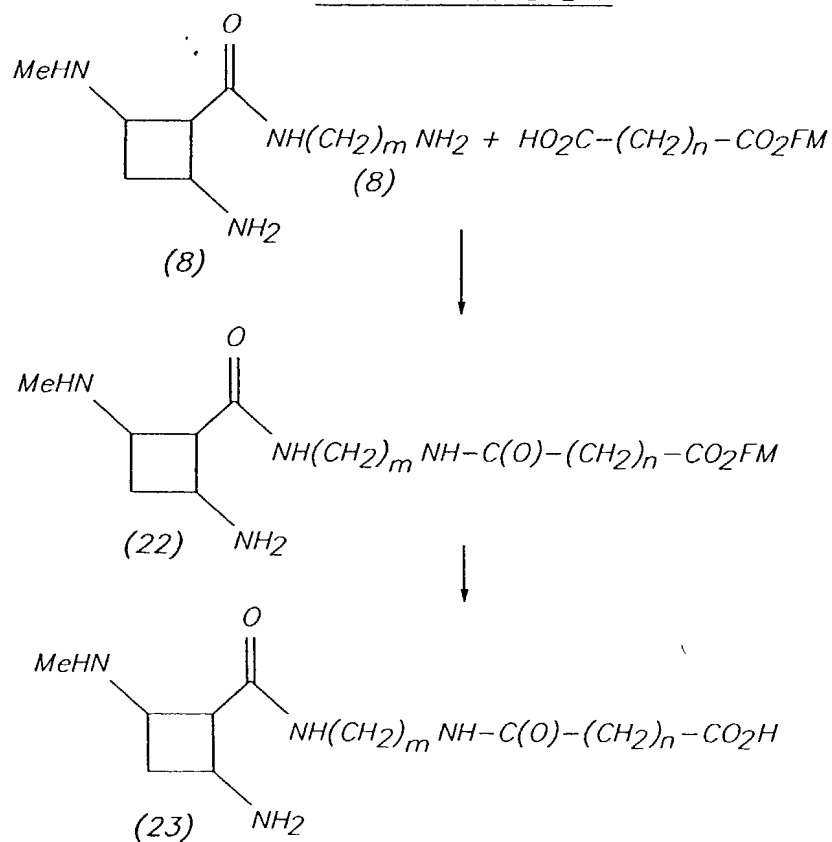


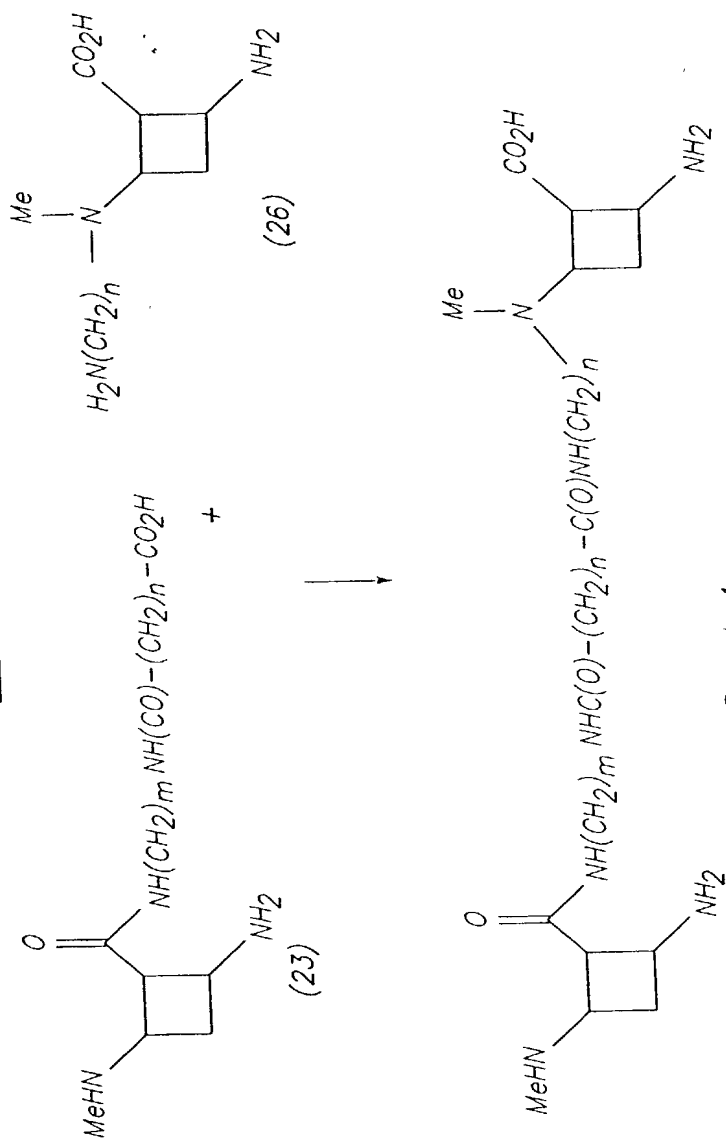
FIG. 6



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REACTION SCHEME 10



Formula 1

FIG. 9

Formula 1

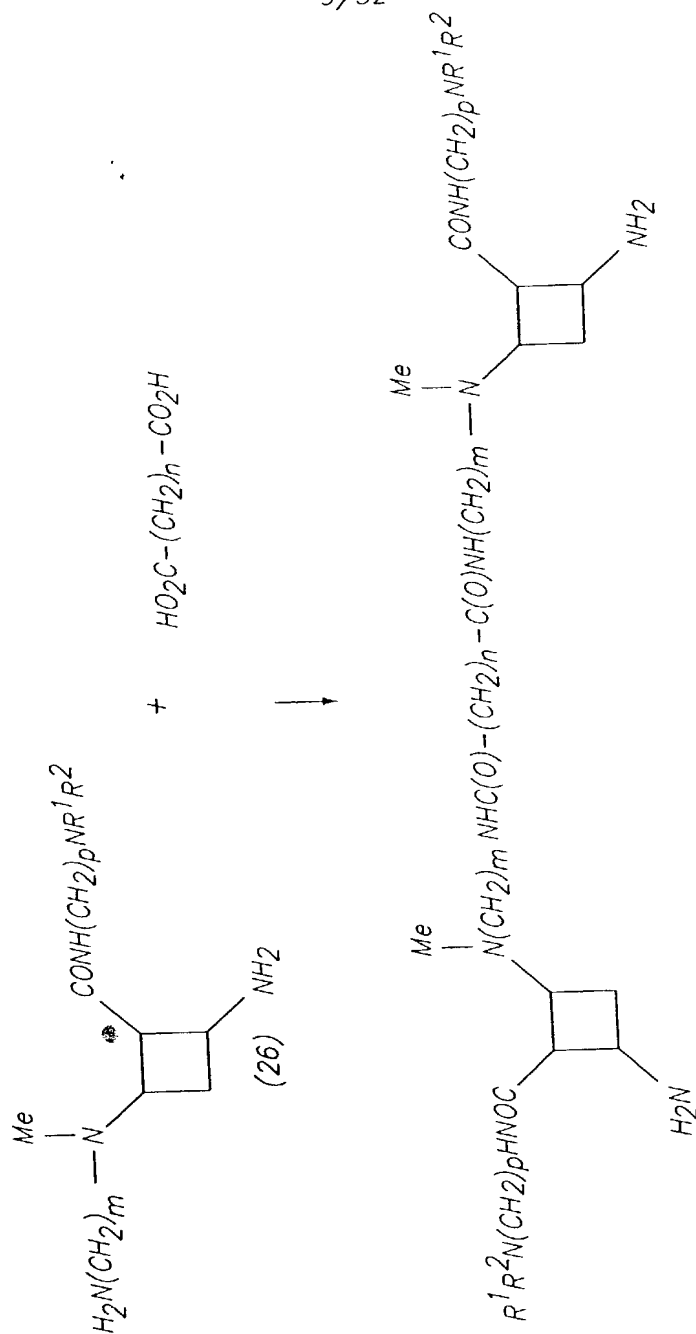


FIG. 11

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FIG. 12

Examples of dimeric display

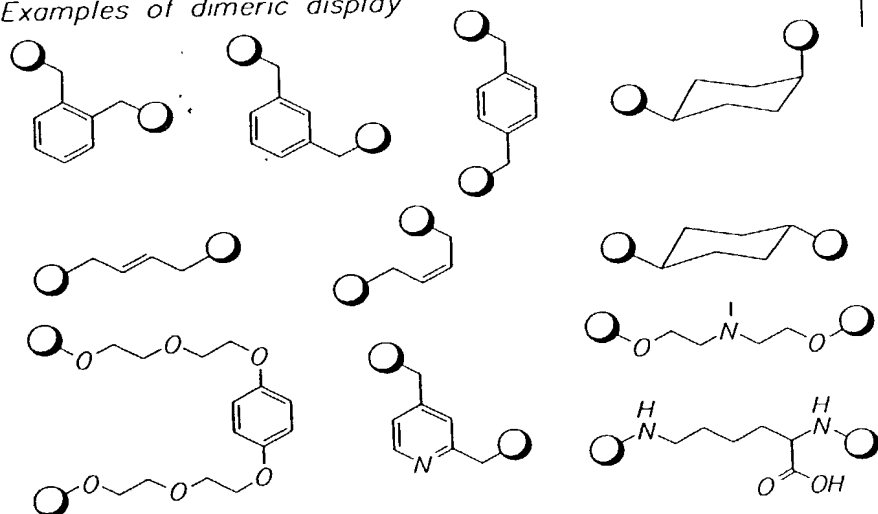
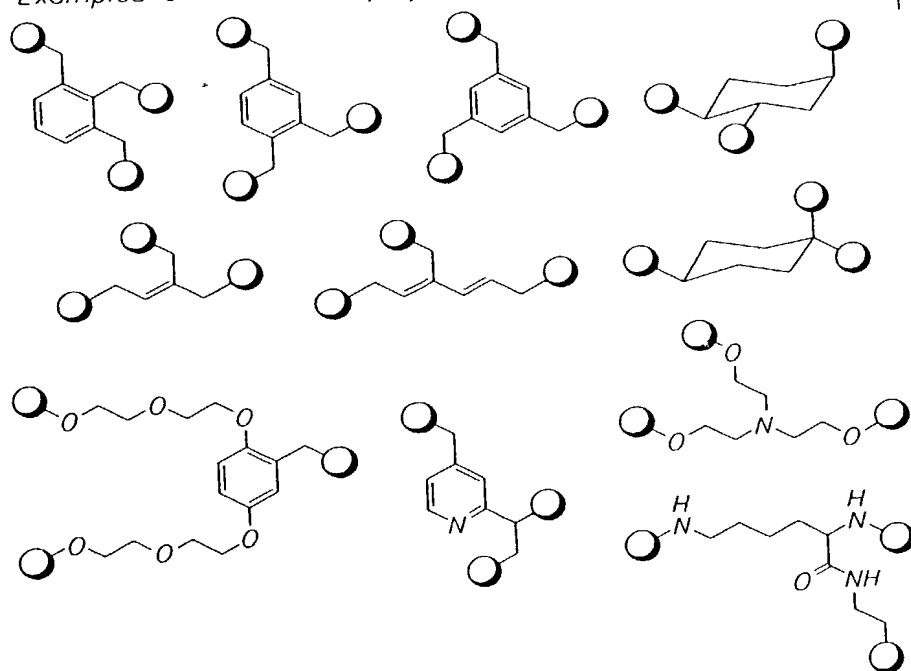
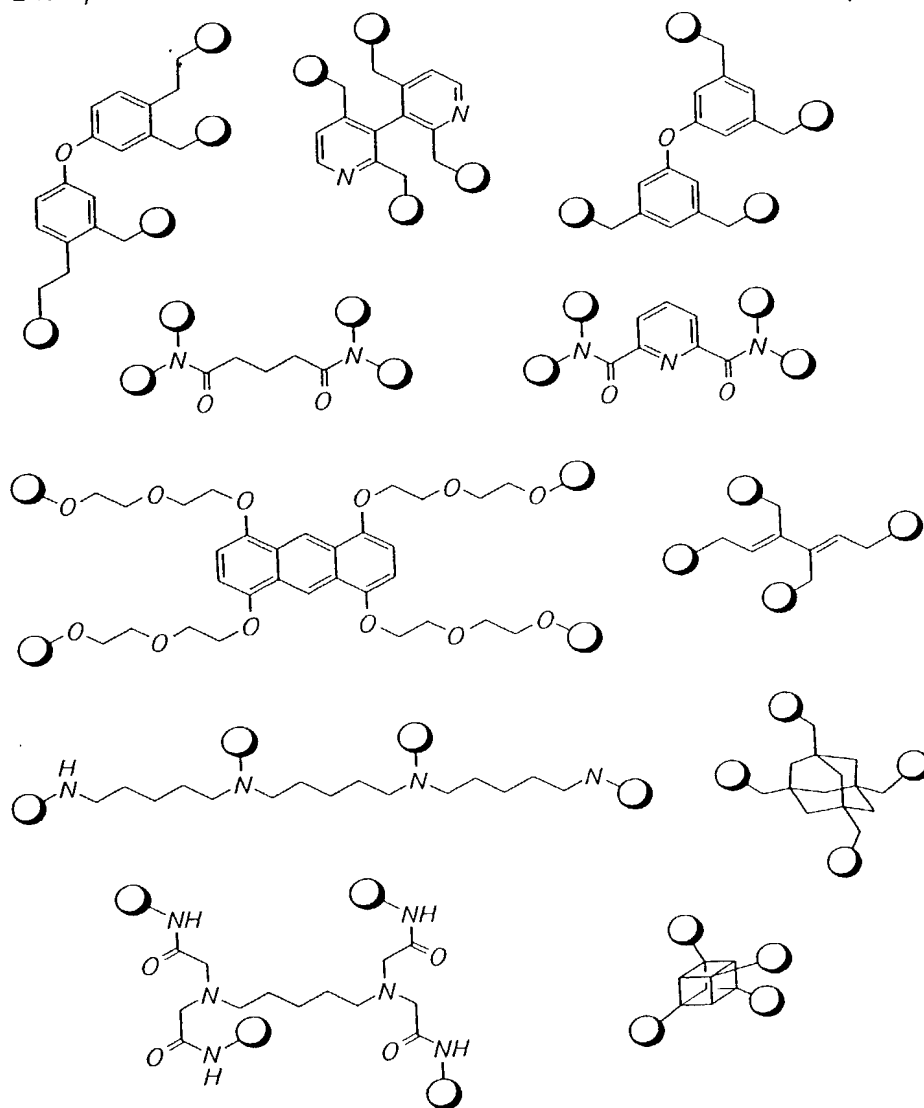


FIG. 13

Examples of trimeric display



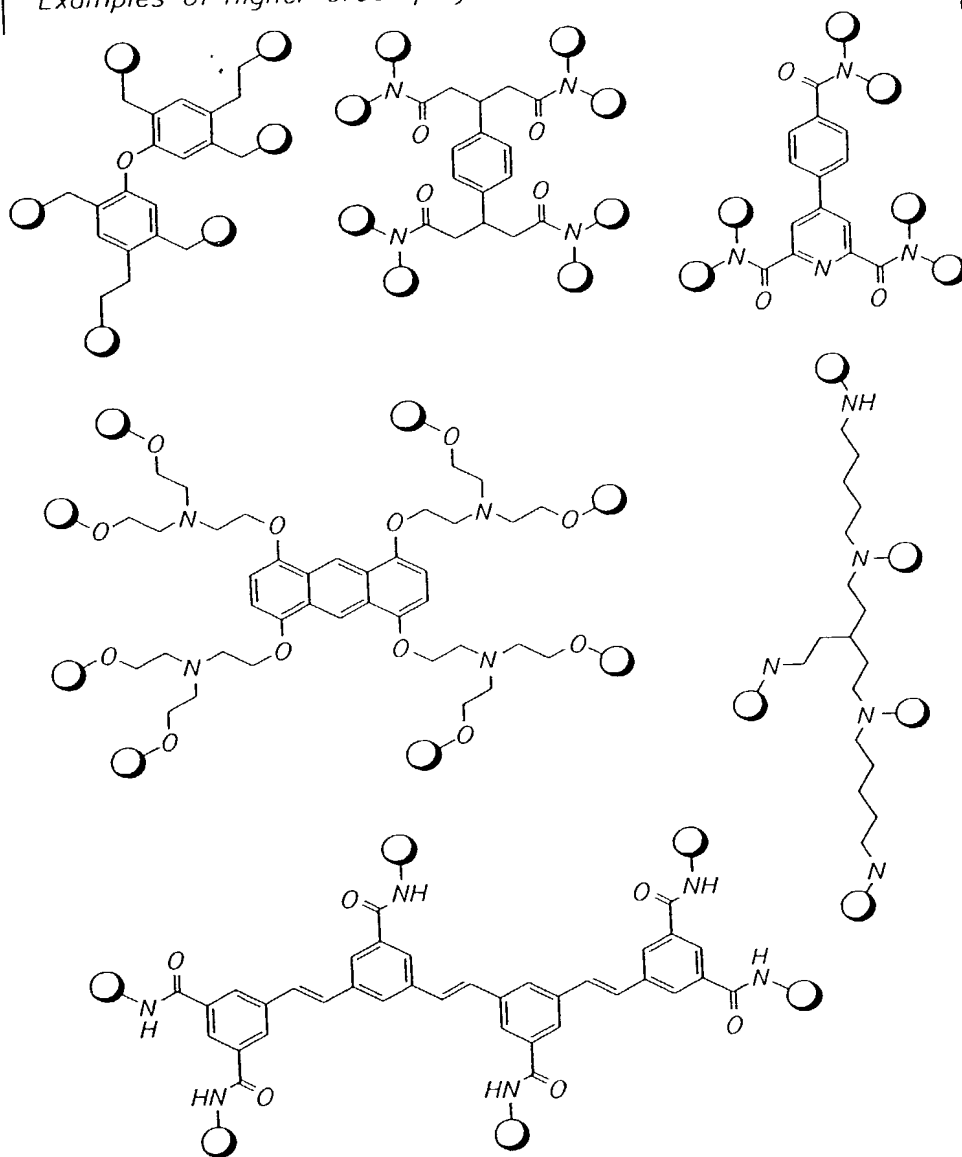
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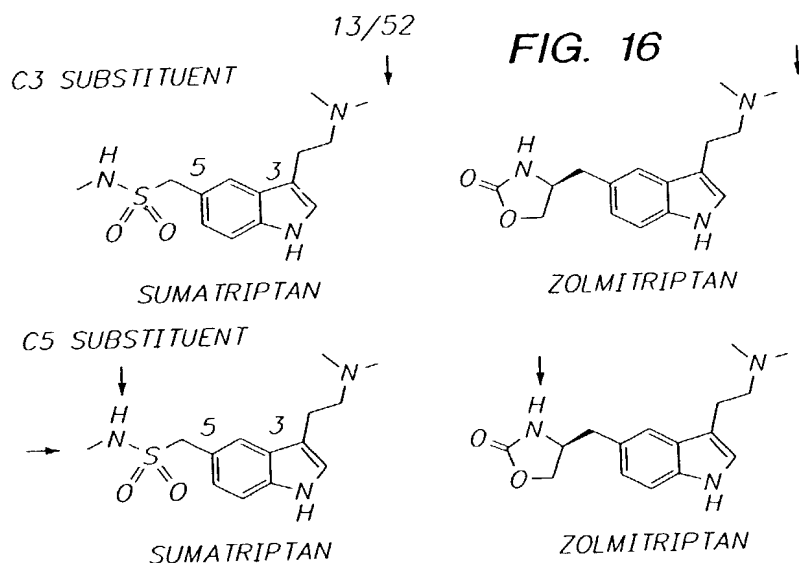
FIG. 14*Examples of tetrameric display*

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FIG. 15

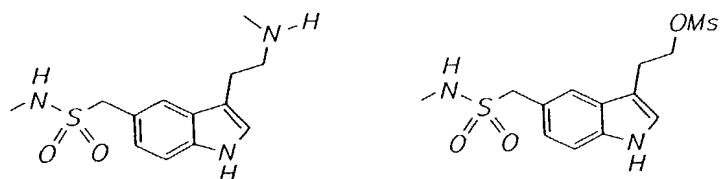
Examples of higher order polyvalent display



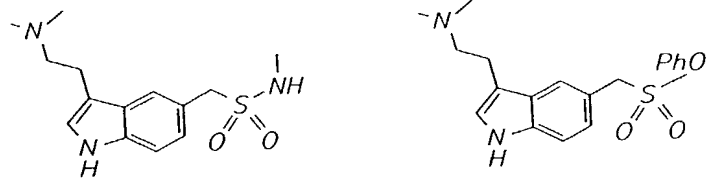
**FIG. 17**

SUMATRIPTAN BUILDING BLOCKS

C3PharmacophoricBuilding Blocks



C5PharmacophoricBuilding Blocks



Pharmacophoric Building Blocks that contain a Spacer

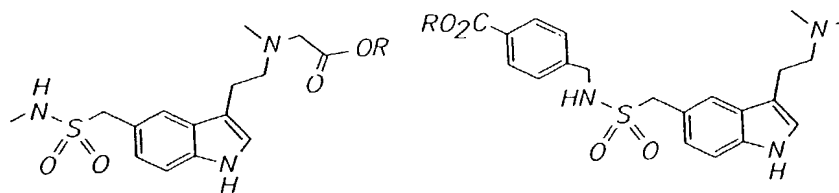
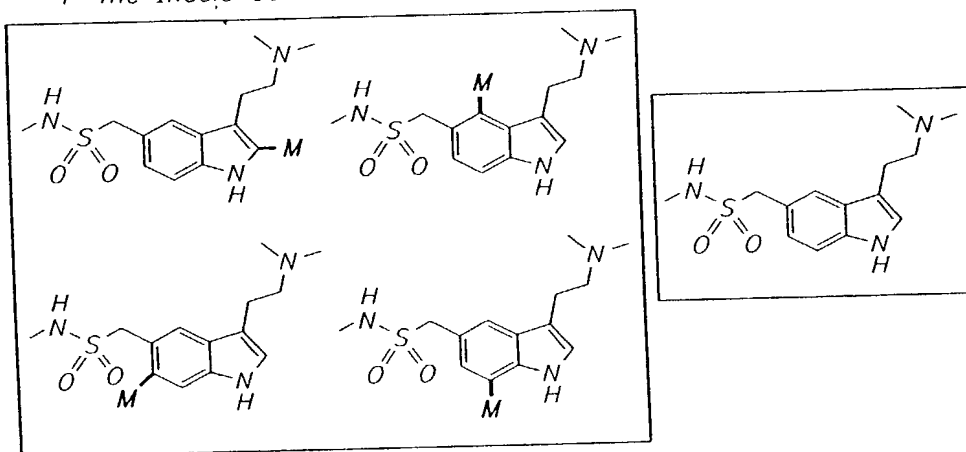


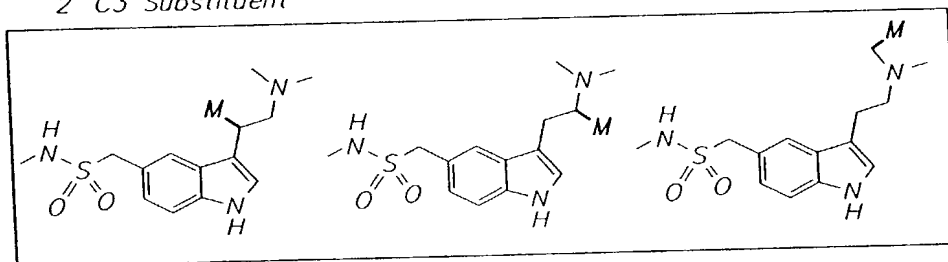
FIG. 18

MULTIVALOMERS OF SUMATRIPTAN

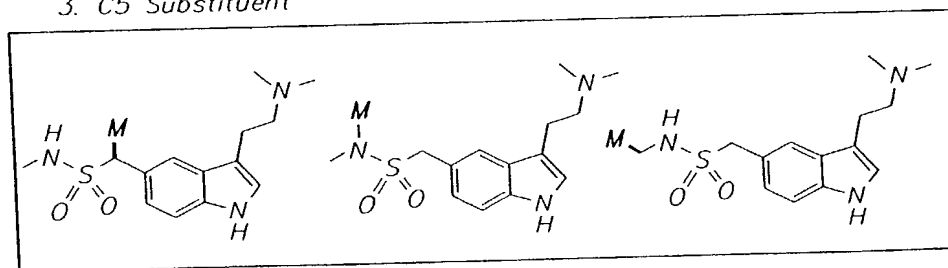
1 The Indole Core



2 C3 Substituent

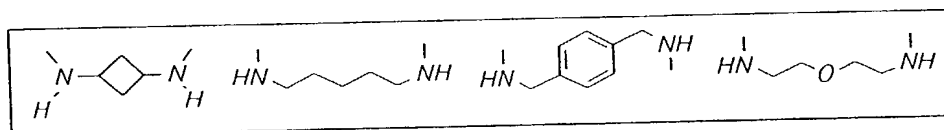
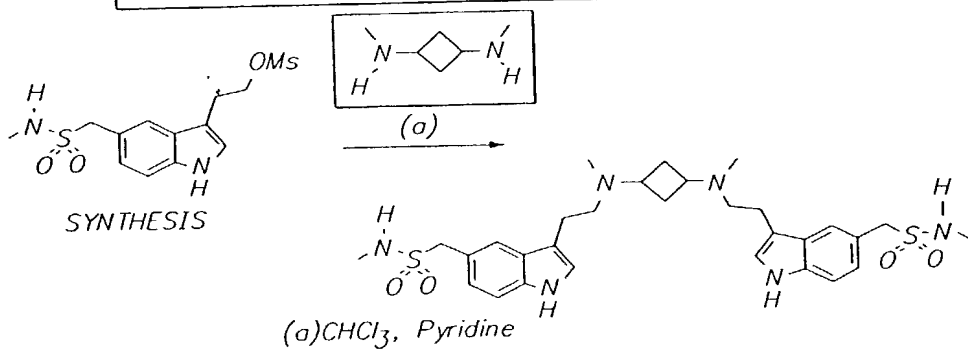


3. C5 Substituent

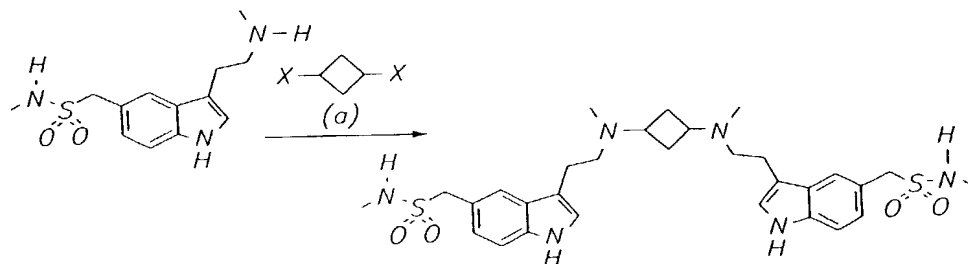


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C3 ELECTROPHILE TO PROVIDE MULTIVALOMERS



C3 NUCLEOPHILE TO PROVIDE MULTIVALOMERS



$X = -\text{CH}_2\text{Br}$ (a) DCM, pyridine

$X = -\text{CHO}$ (a) DCM, $\text{NaBH}(\text{OAc})_3$, AcOH

$X = -\text{CO}_2\text{H}$ (a) DIC, DIPEA, DMF

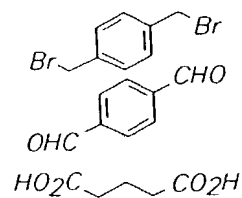
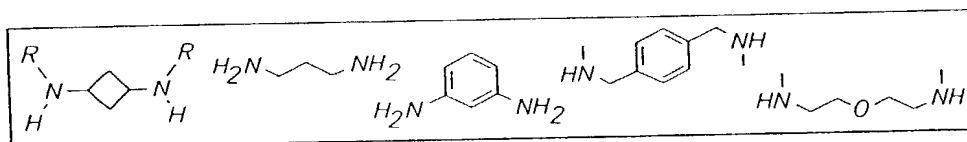
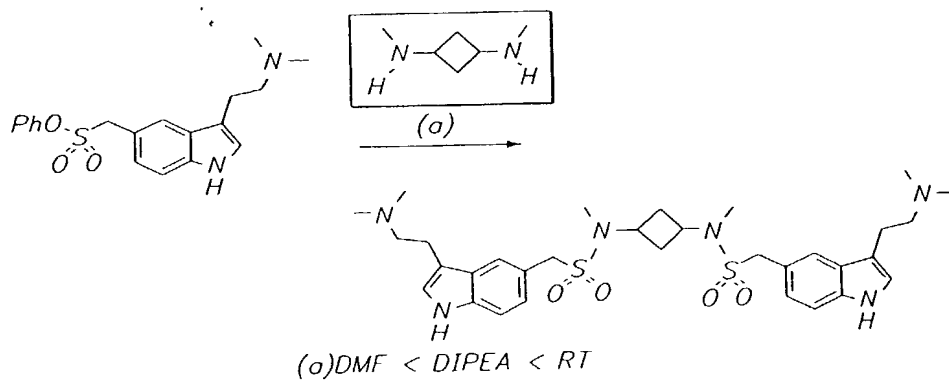


FIG. 19

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C5 FUNCTIONALIZATION OF SUMATRIPTAN

Electrophilic Pharmacophoric Monovalomer



Nucleophilic Pharmacophoric Monovalomer

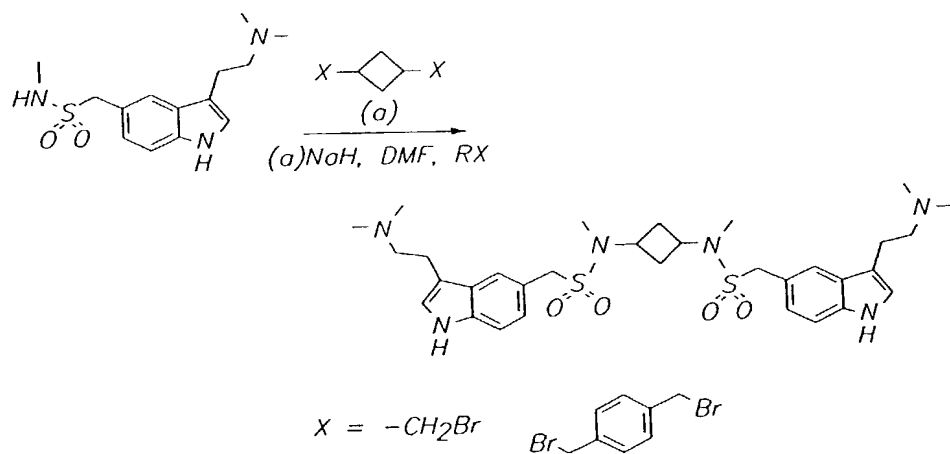


FIG. 20

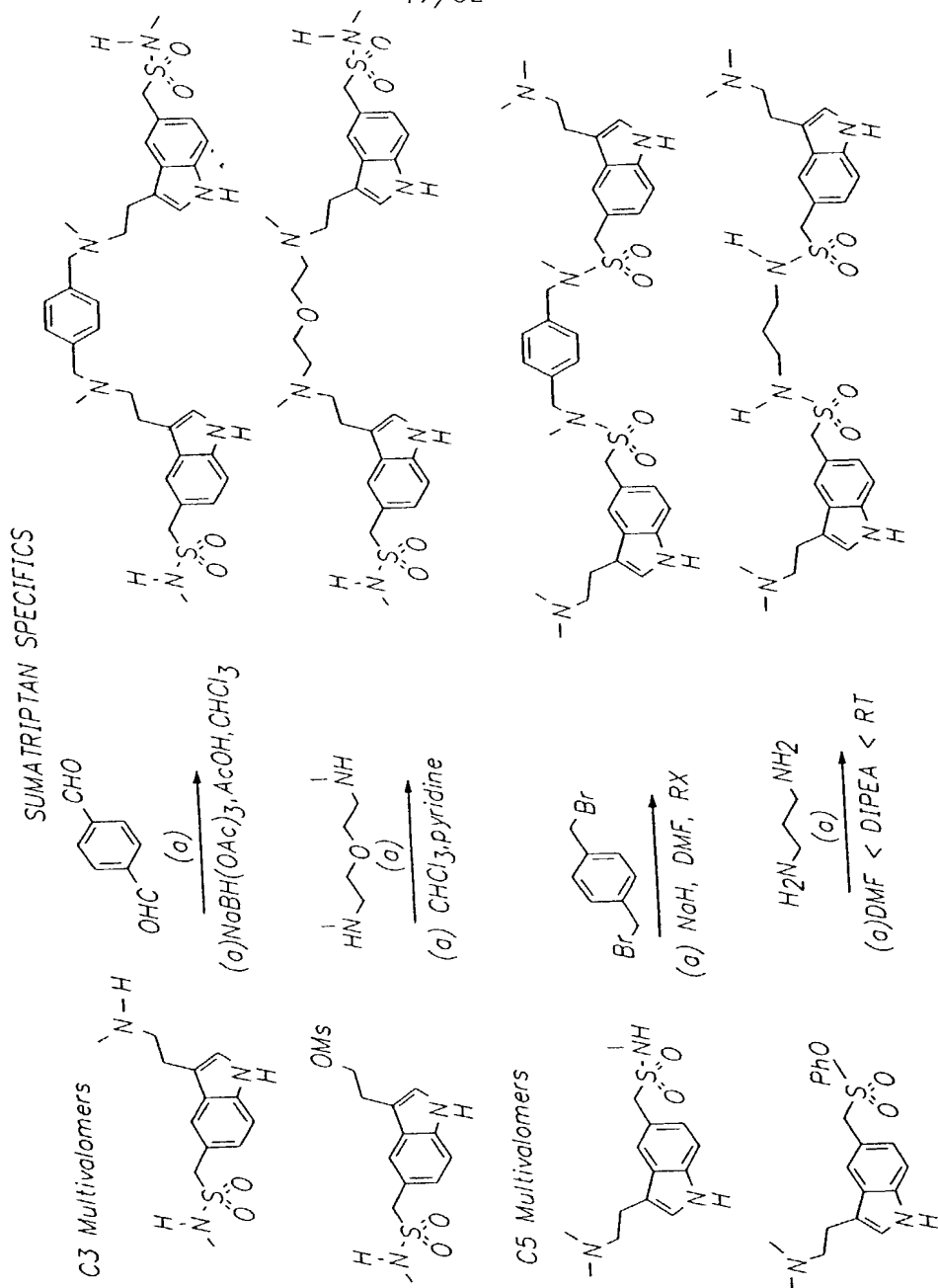


FIG. 21

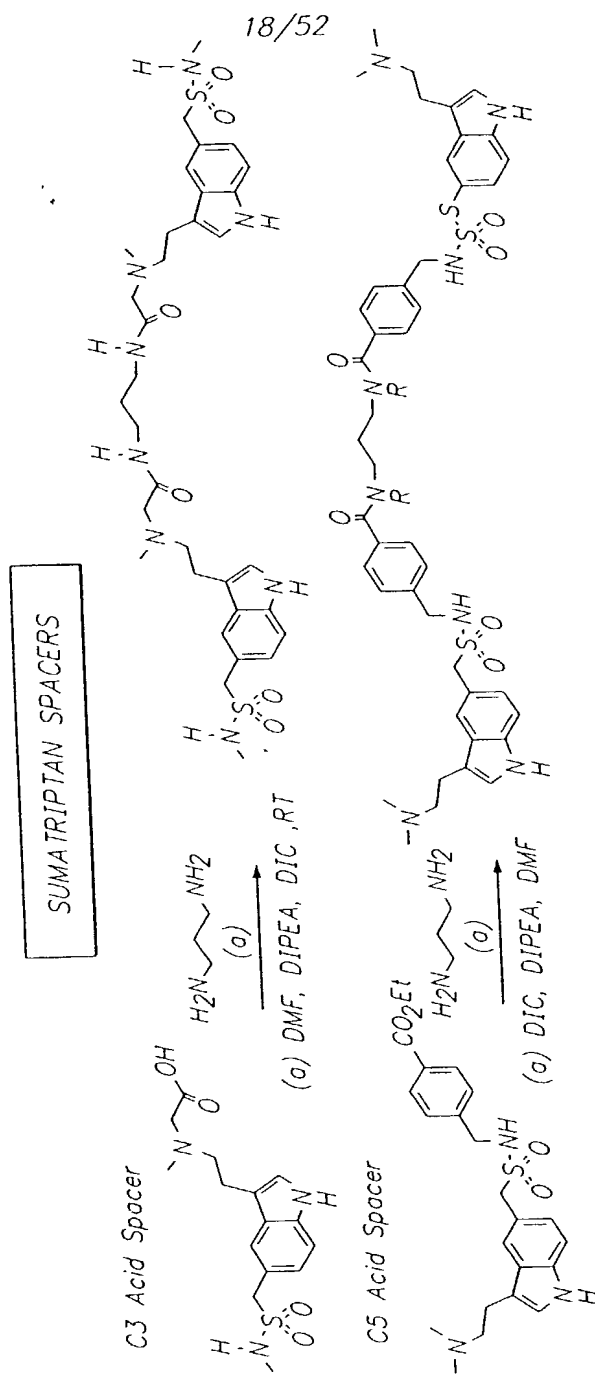
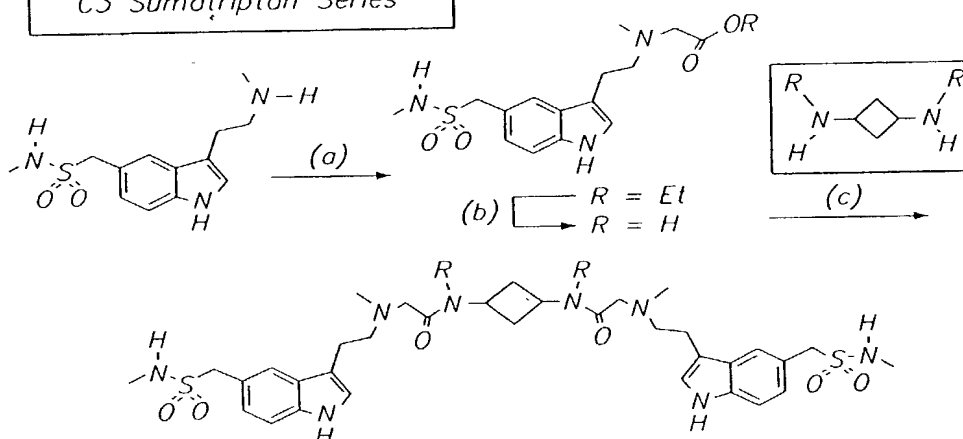


FIG. 22

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Introduction of Spacer To Facilitate Multivalomer Formation

C3 Sumatriptan Series



C5 Sumatriptan Series

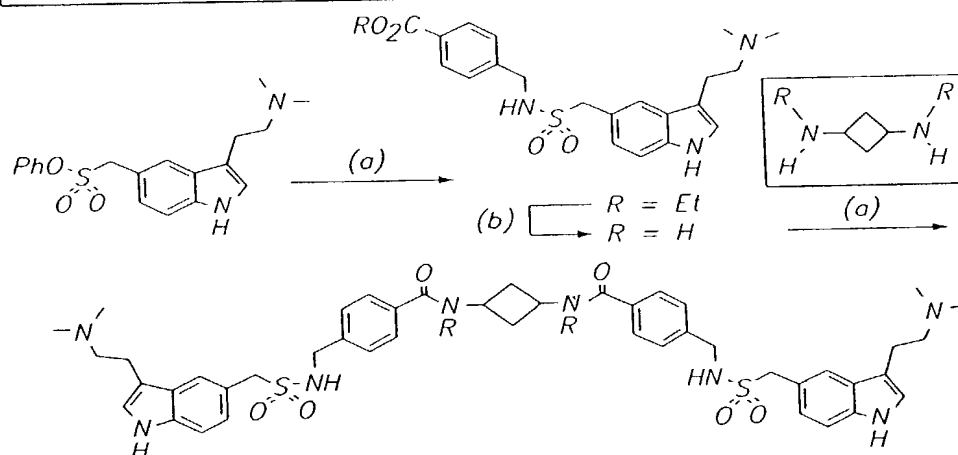
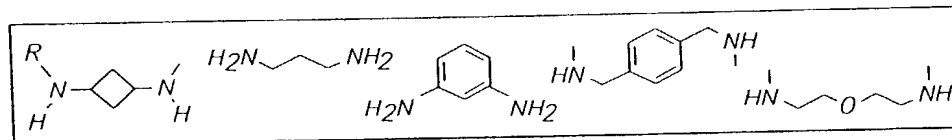
(a) DIPEA, DCM, $\text{BrCH}_2\text{CO}_2\text{Et}$ (b) LiOH , THF, H_2O , (c) DIC, DIPEA, DMF

FIG. 23

MUSCARINIC ANTAGONISTS USED IN AIRWAY DISEASE

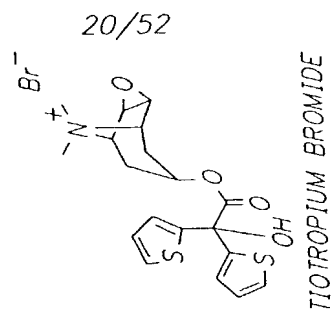
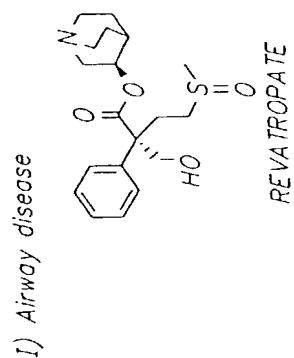
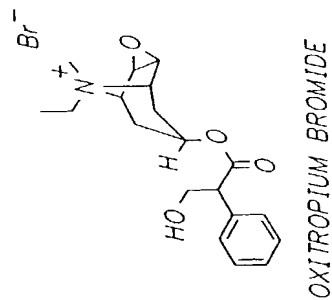
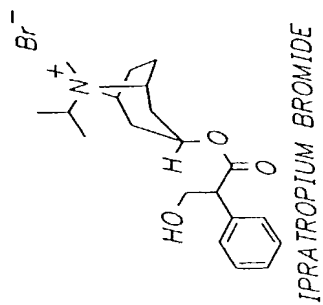
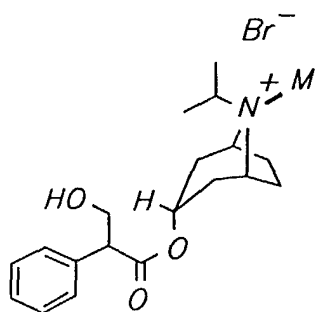


FIG. 24

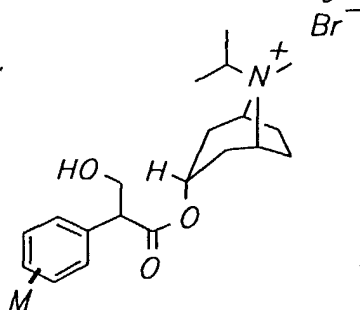
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SITES FOR DIMERIZATION

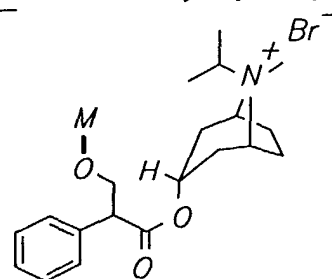
Nitrogen Atom of Tropane Core



Aromatic Ring

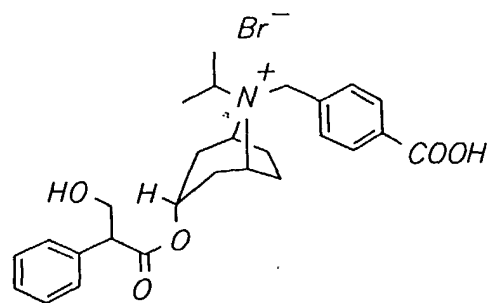
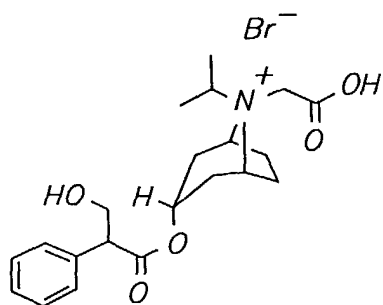


Primary Hydroxyl



Suitable, Pharmacophoric Building Blocks

*Nitrogen Atom of Tropane Core
Acid Series*



Amine Series

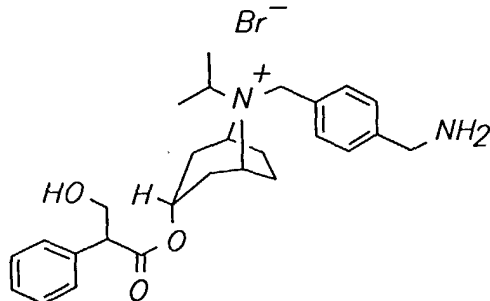
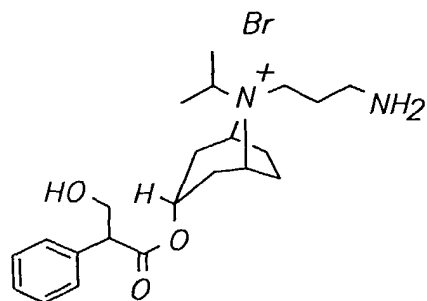
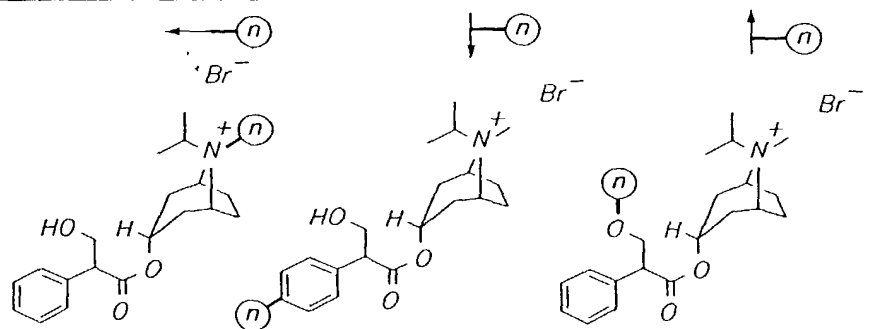


FIG. 25

Ipratropium Multivalomers 1- Different points of Attachment



n defines the valency of the multivomer
 ○ defines the framework core
 → distinguishes the differing points of attachment of ipratropium

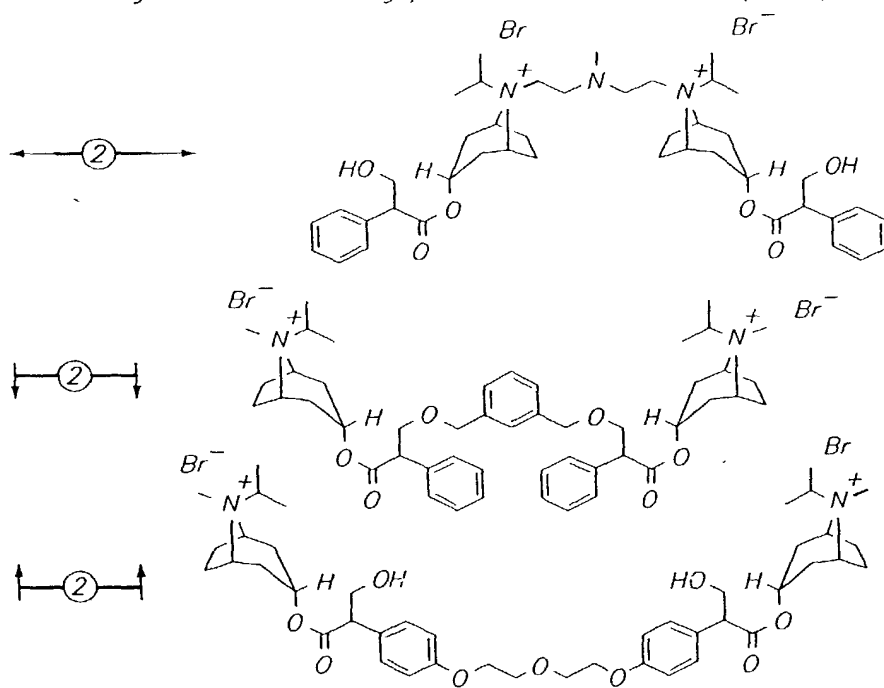


FIG. 26

Ipratropium Multivalomers 2-Alternative Framework Cores

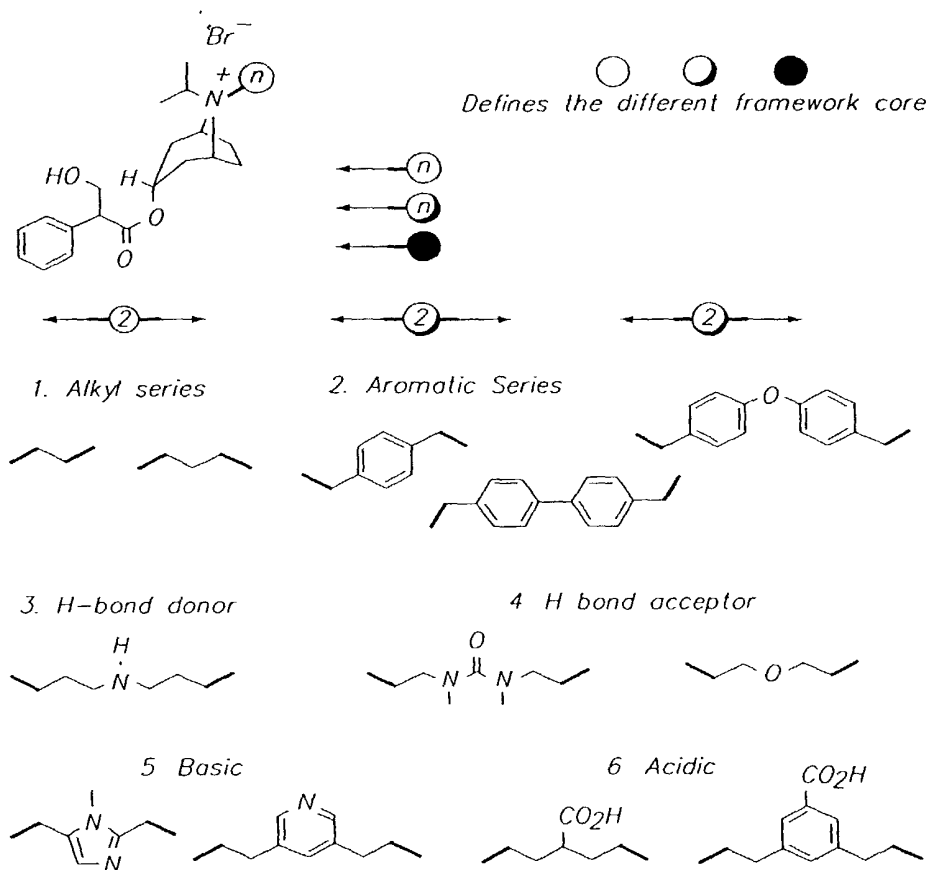


FIG. 27

FIG. 28

Ipratropium Multivalomers 4-Relative Pharmacophore Orientation

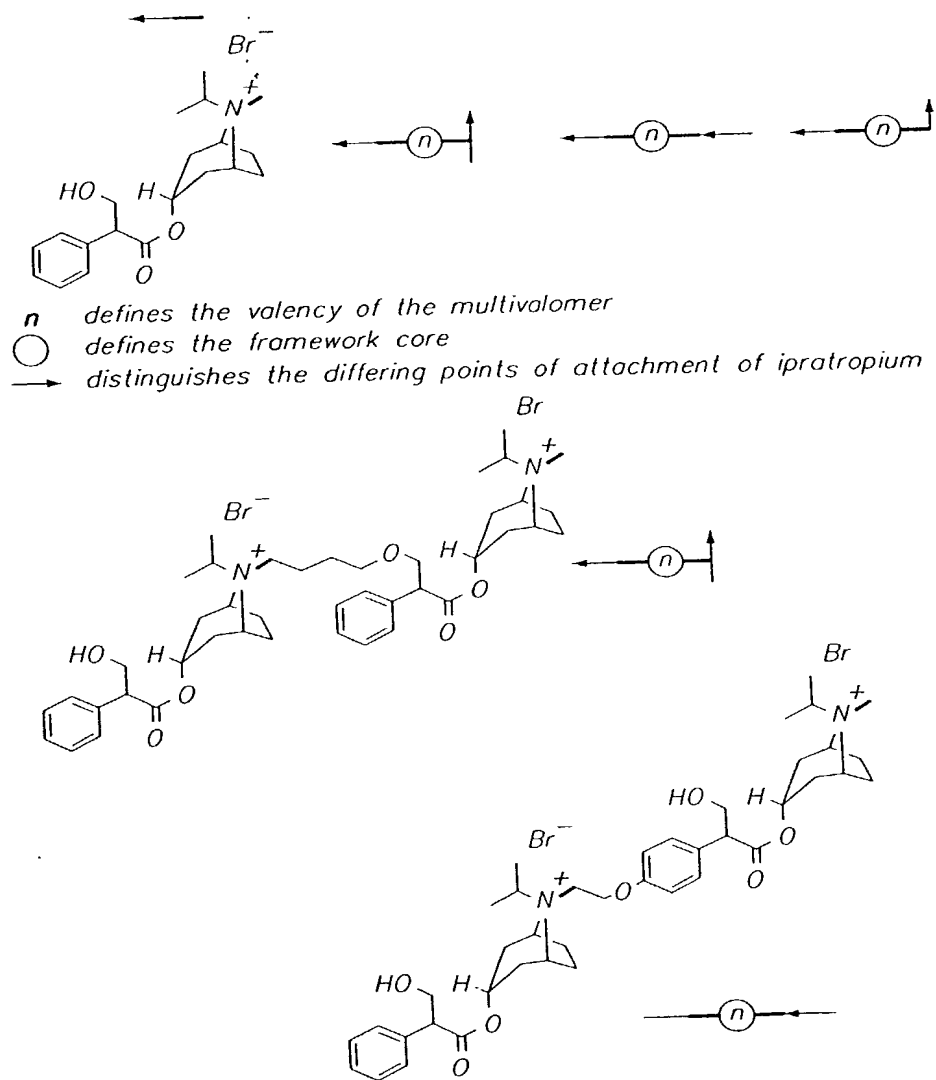
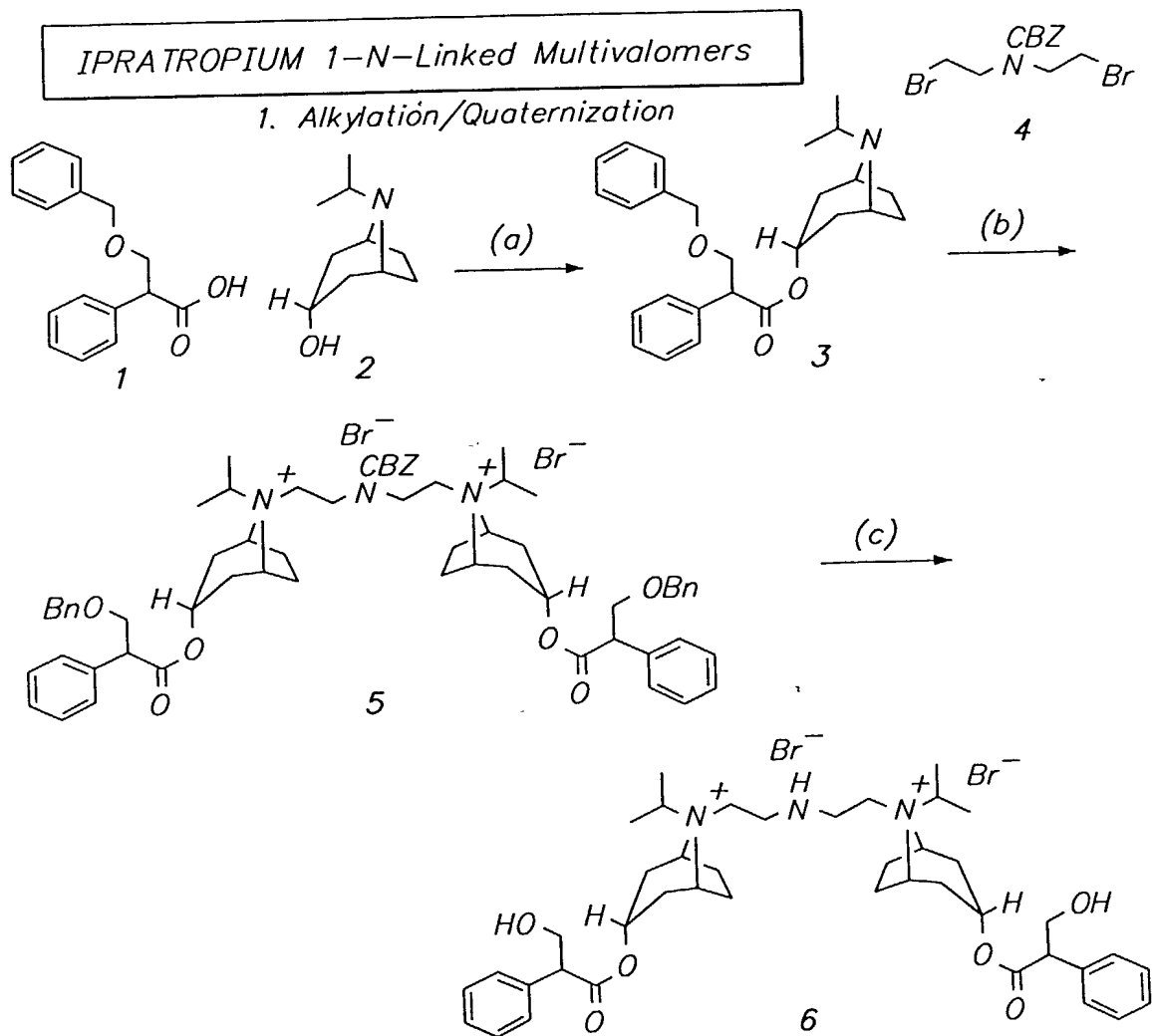


FIG. 29

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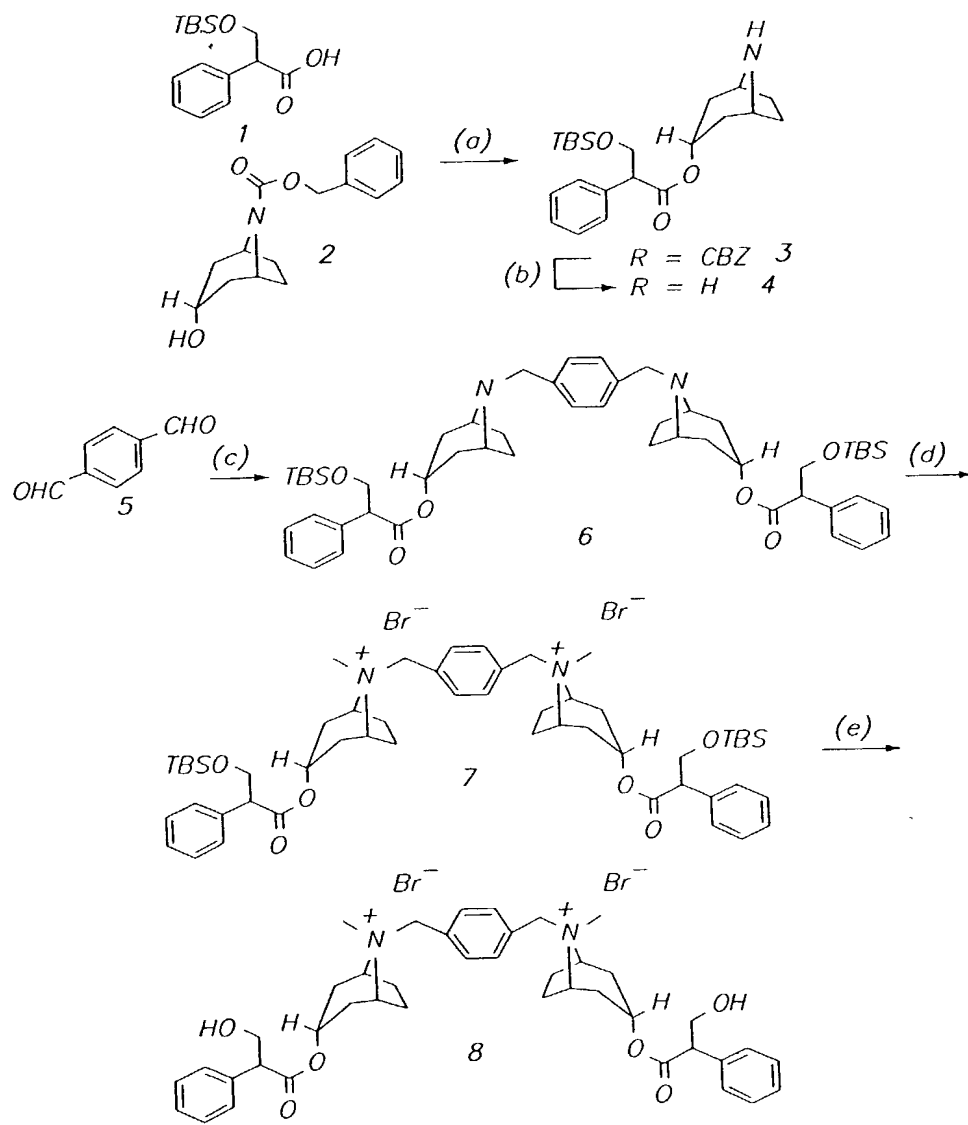


(a) DIC, DMAP, DMF (b) CHCl_3 (c) Pd/C, H_2 , EtOAc

FIG. 30

IPRATROPIUM 2-N-Linked Multivalomers

1. Reductive Amination/Quaternization

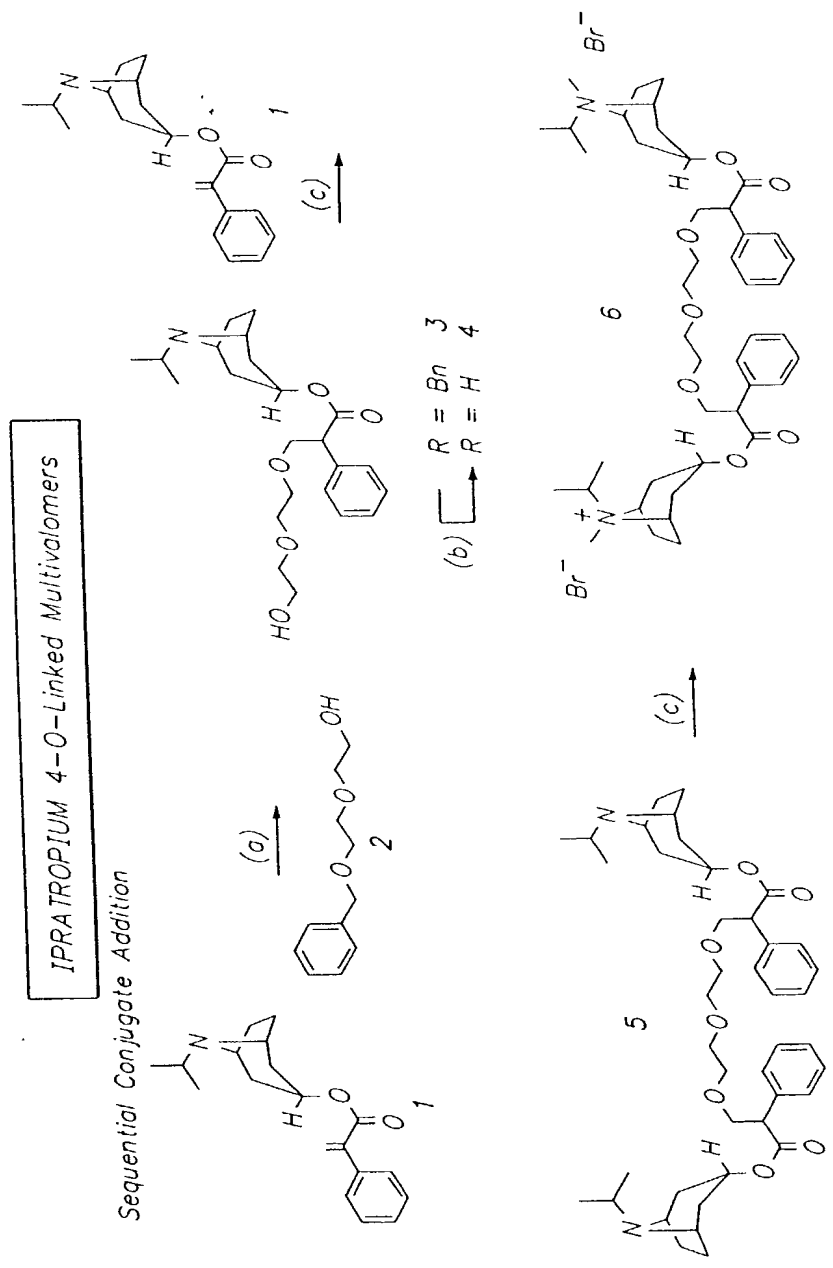


(a) DIC, DMF, DMF (b) Pd/C, H₂, EtOAc (c) NaBH(OAc)₃, CHCl₃, AcOH
(d) MeBr, CHCl₃ (e) TBAF, THF

FIG. 31

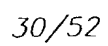
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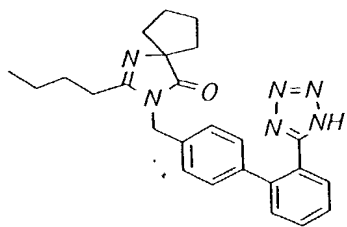


(a) NaH, DME, heat (b) Pd/C, H₂, EtOAc (c) NaH, DME, heat (d) MeBr, CHCl₃, heat

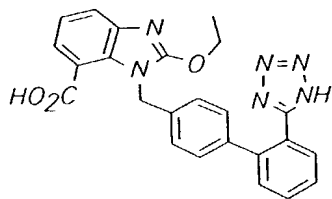
FIG. 33



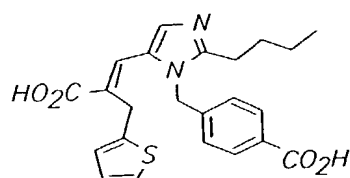
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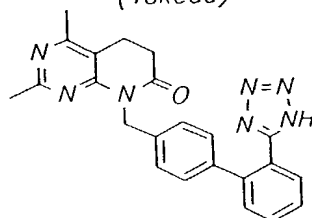
IRBESARTAN
(Sanofi)



CANDESARTAN (Atacand)
(Takeda)

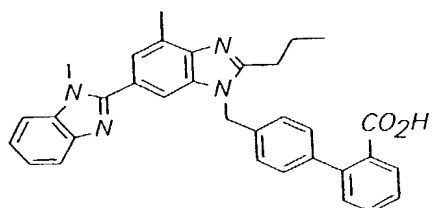


EPROSARTAN (Tevetan)
(Smith KlineBeecham)

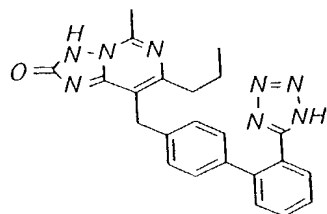


TASOSARTAN (Verdia)
(Wyeth-Ayerst)

FIG. 35



TELMISARTAN
(Boehringer Ingelheim)
Phase III



RIPISARTAN
(Bristol Myers Squibb)
Phase II

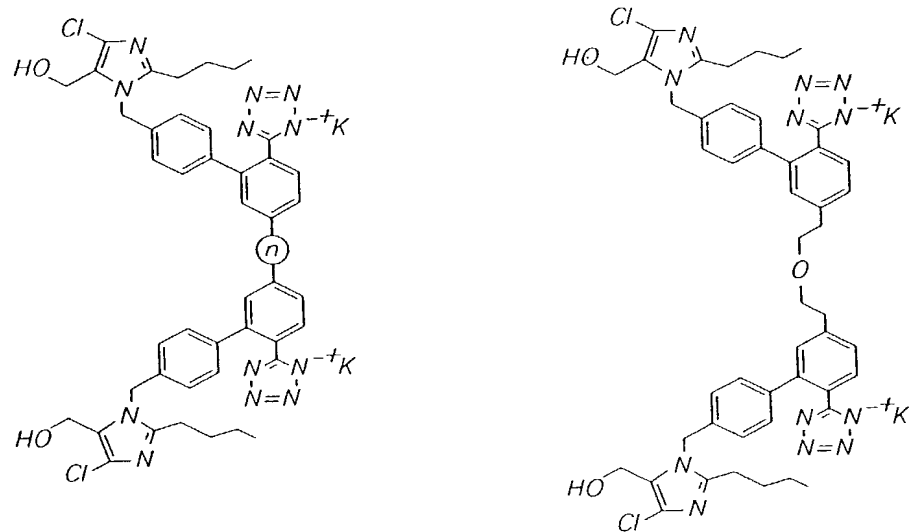
Phase II
CS-866 Sankyo
DA-727 Daiichi
KRH-594 Wakunaga
LR-B/081 Lusofarmaco
TAK-536 Takeda
YM-358 Yamanouchi

FIG. 36

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Losartan Multivalomers 1-Differing Points of Attachment

1. Aryl Linked Multivalomers



2. Butyl Linked Multivalomers

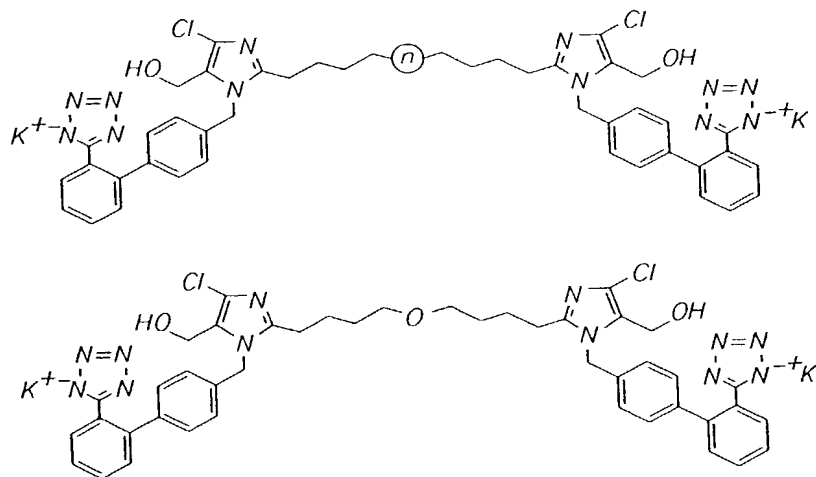


FIG. 38

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Lorsartan Multivalomers 2-Differing Valency of Multivalomer

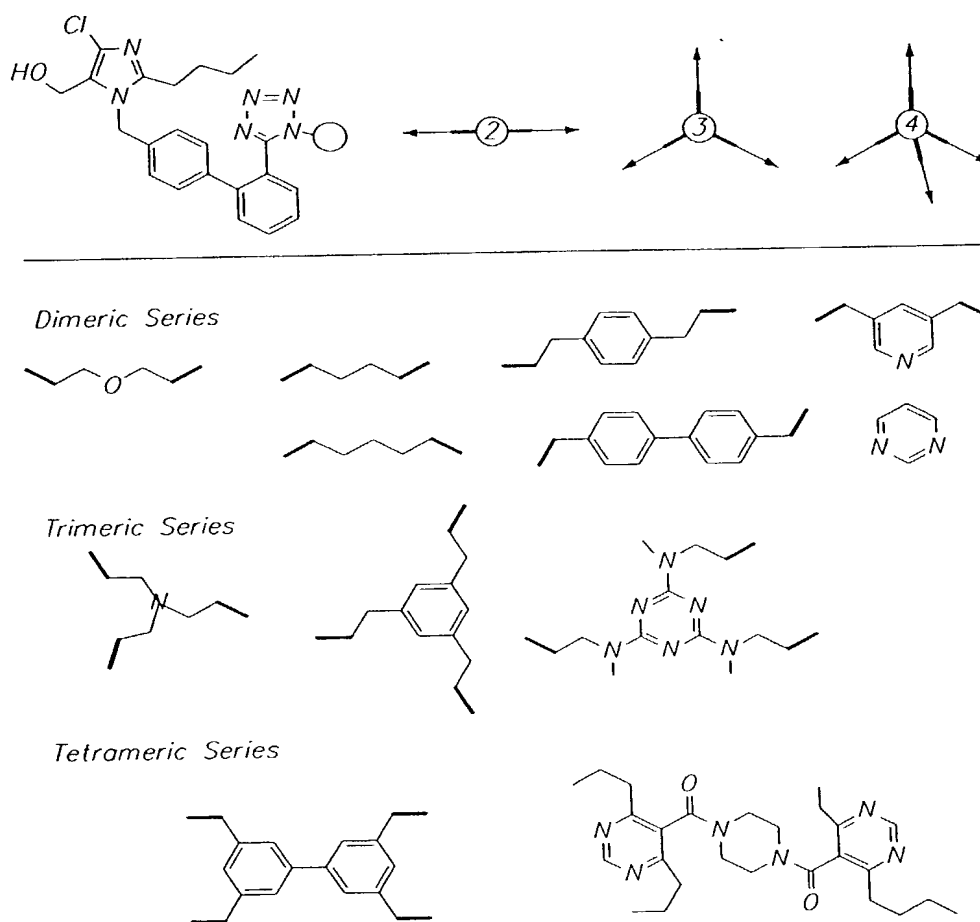
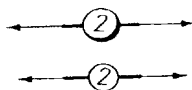
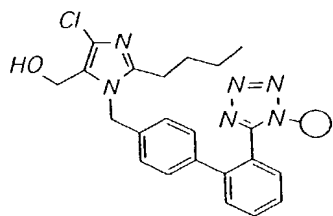


FIG. 40

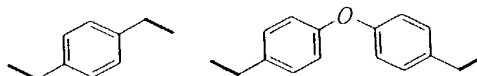
Lorsartan Multivalomers 3-Differing Framework Building Blocks



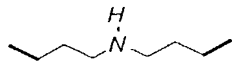
1. Alkyl Series



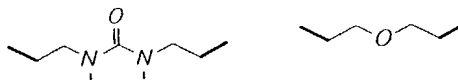
2. Aromatic Series



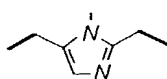
3 H-bond donor



4 H bond acceptor



5 Basic



6 Acidic

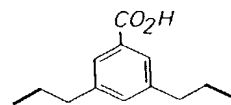
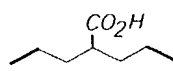
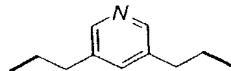


FIG. 41

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Losartan Multivalomers 5-Heterovalomers

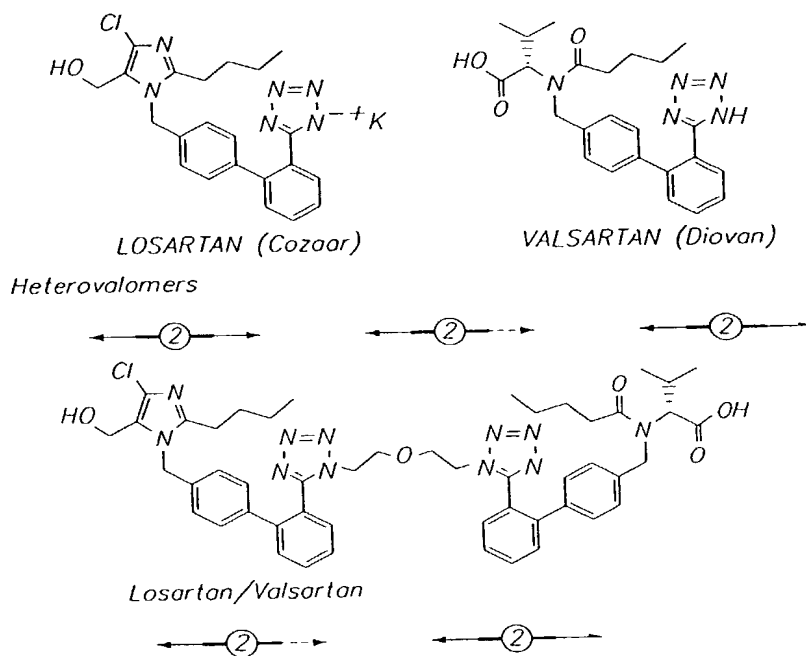


FIG. 43

Losartan Multivalomers Synthesis 1-Hydroxyl Linked Multivalomer

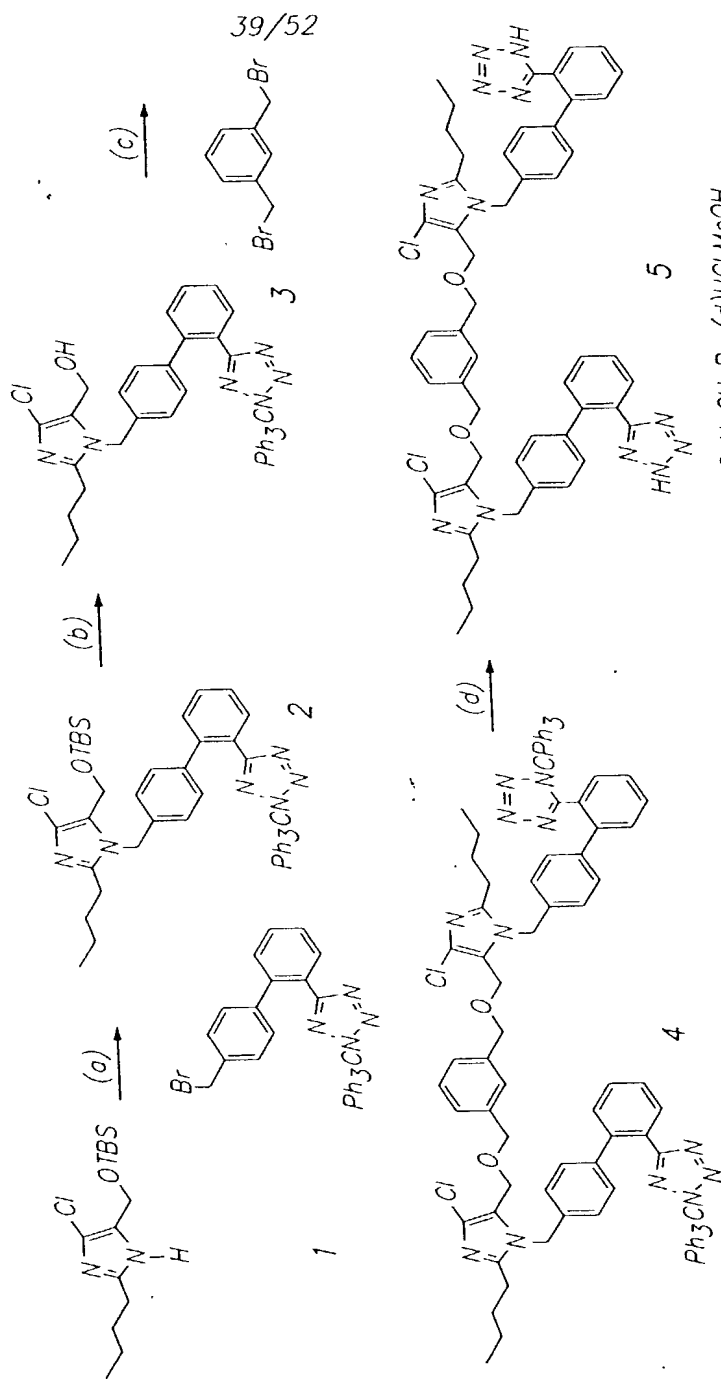


FIG. 44

Losartan Multivalomer Synthesis 2-Hydroxyl Linked Multivalomer

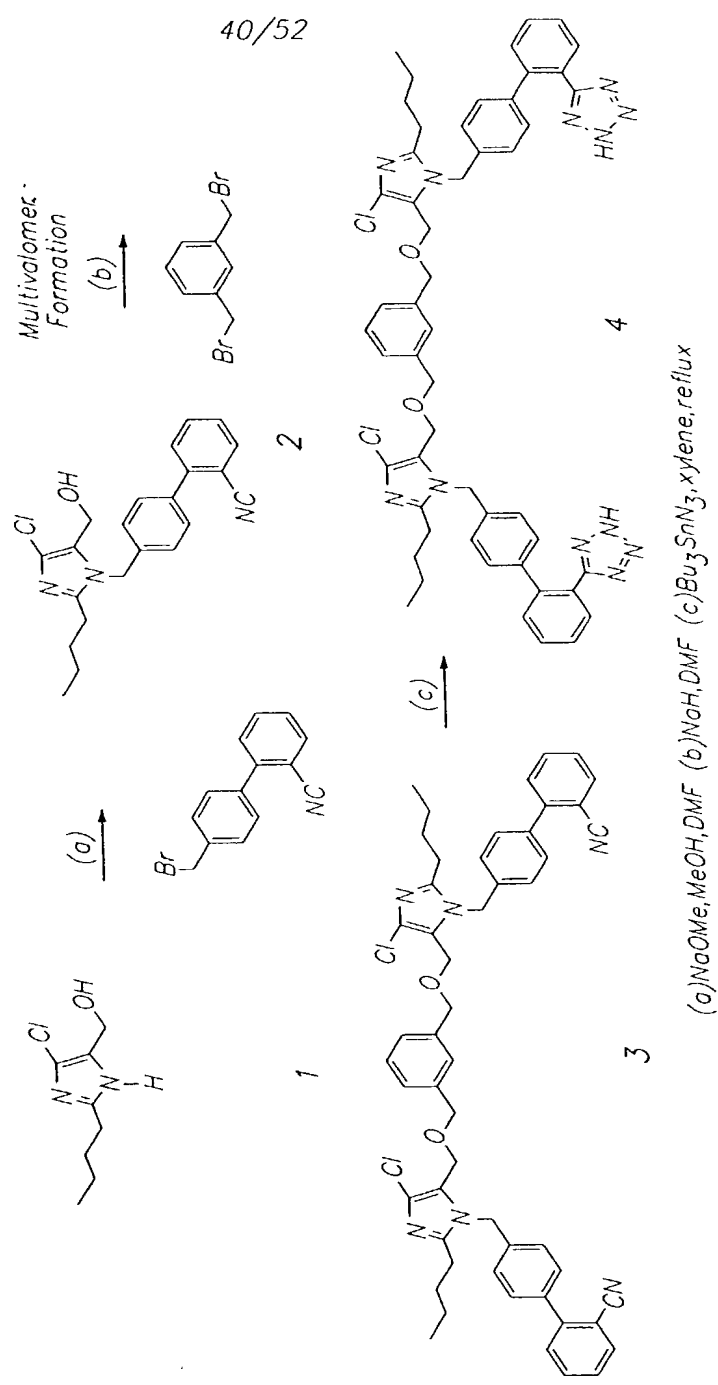
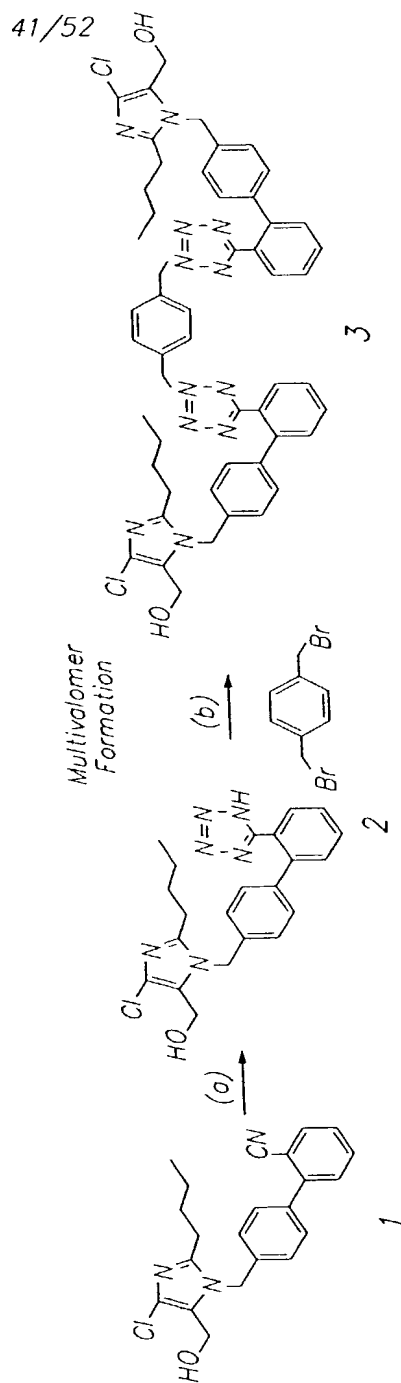


FIG. 45

Losartan Multivalomer Synthesis 3-Tetrazole Linked Multivalomers

Strategy-Selective tetrazole alkylation in the presence of the primary hydroxyl



For precedent see Carini, D. J., J. Med. Chem., 1991, 34, 2525-2547

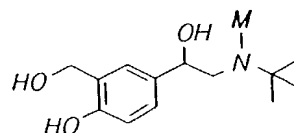
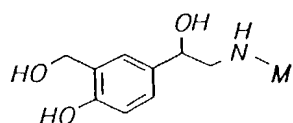
FIG. 46

FIG. 47

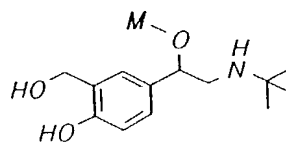
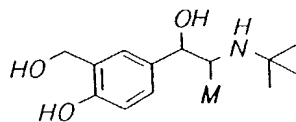
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Albuterol Multivalomers

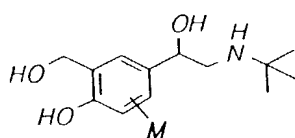
1. N atom



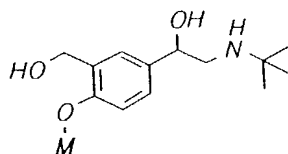
2. Ethanolamine function



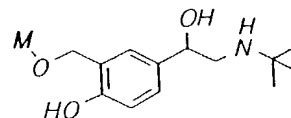
3 Phenyl Ring
New substitution



Phenolic Group



Benzyl Alcohol

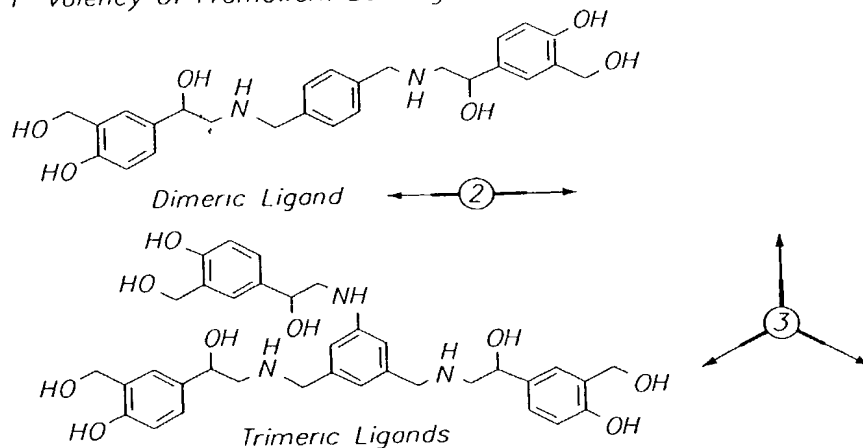


M represents a site for the attachment of the monovalomer to the framework core.

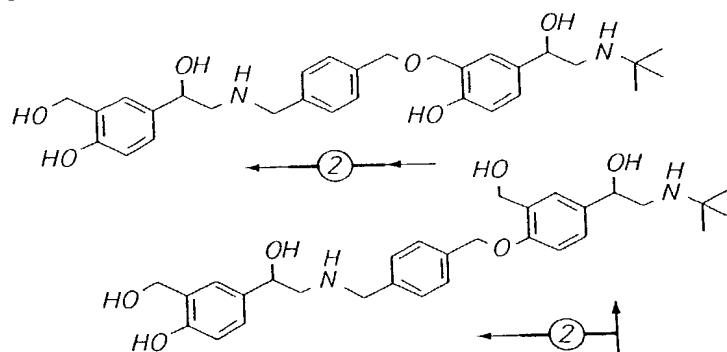
FIG. 48

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1 Valency of Framework Building Block



2. Relative Orientation of Monovalomer Building Blocks



3 Mixed Multivalomers Derived from Different β_2 -agonists

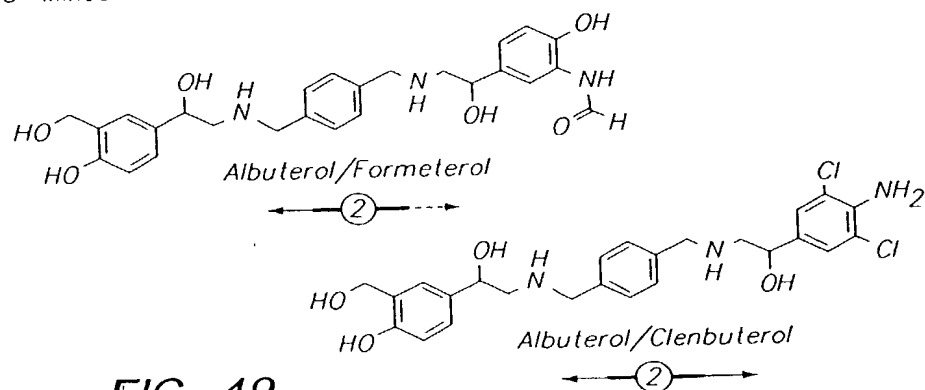


FIG. 49

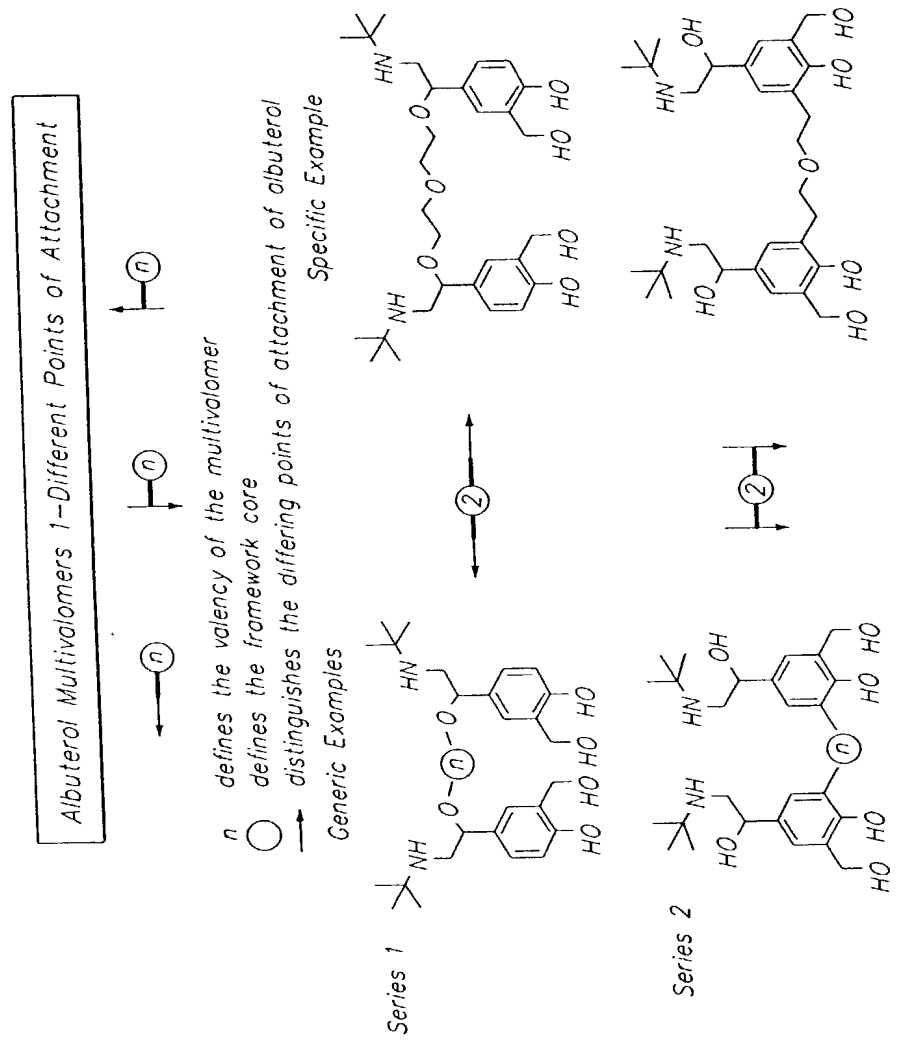


FIG. 50A

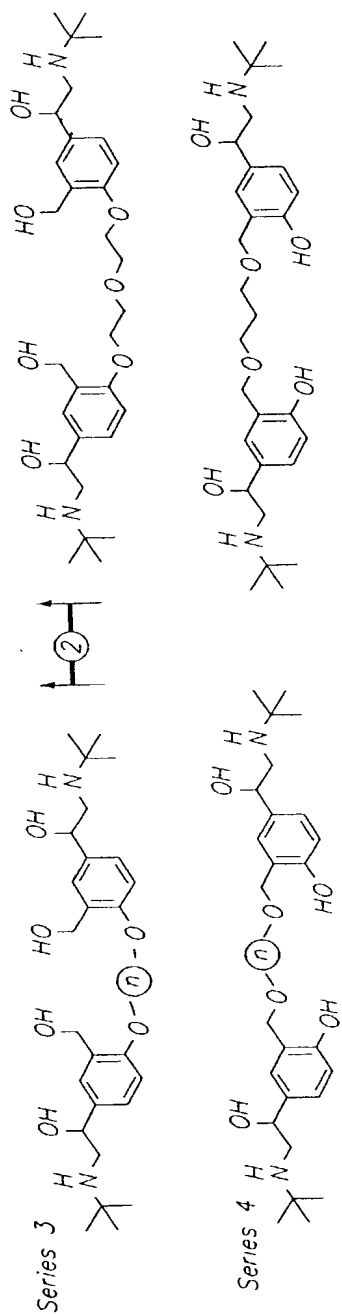


FIG. 50B

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Albuterol Multivalomers 2-Alternative Framework Cores

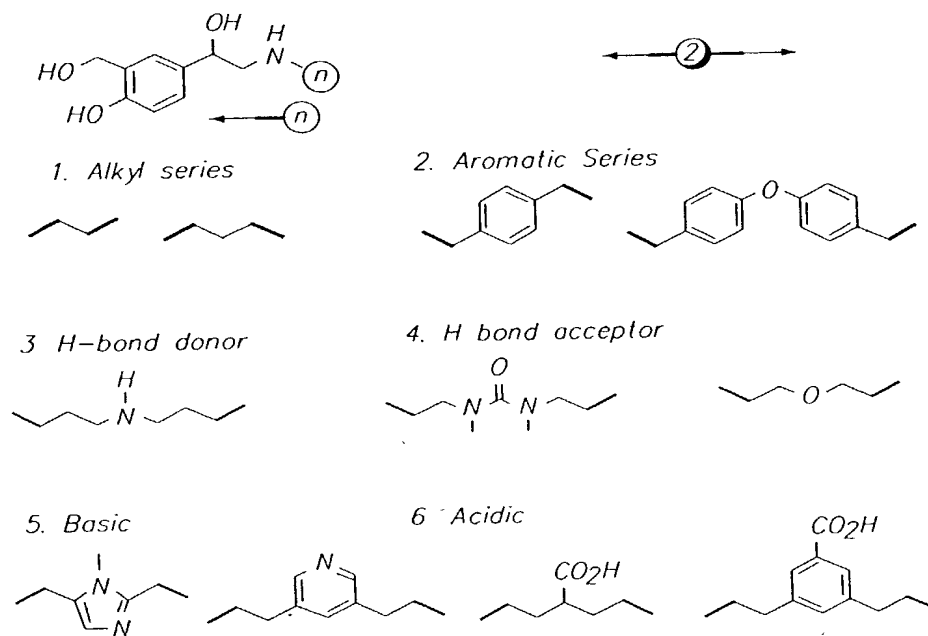


FIG. 51

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Albuterol Multivalomers 3-Alternative Framework Valency

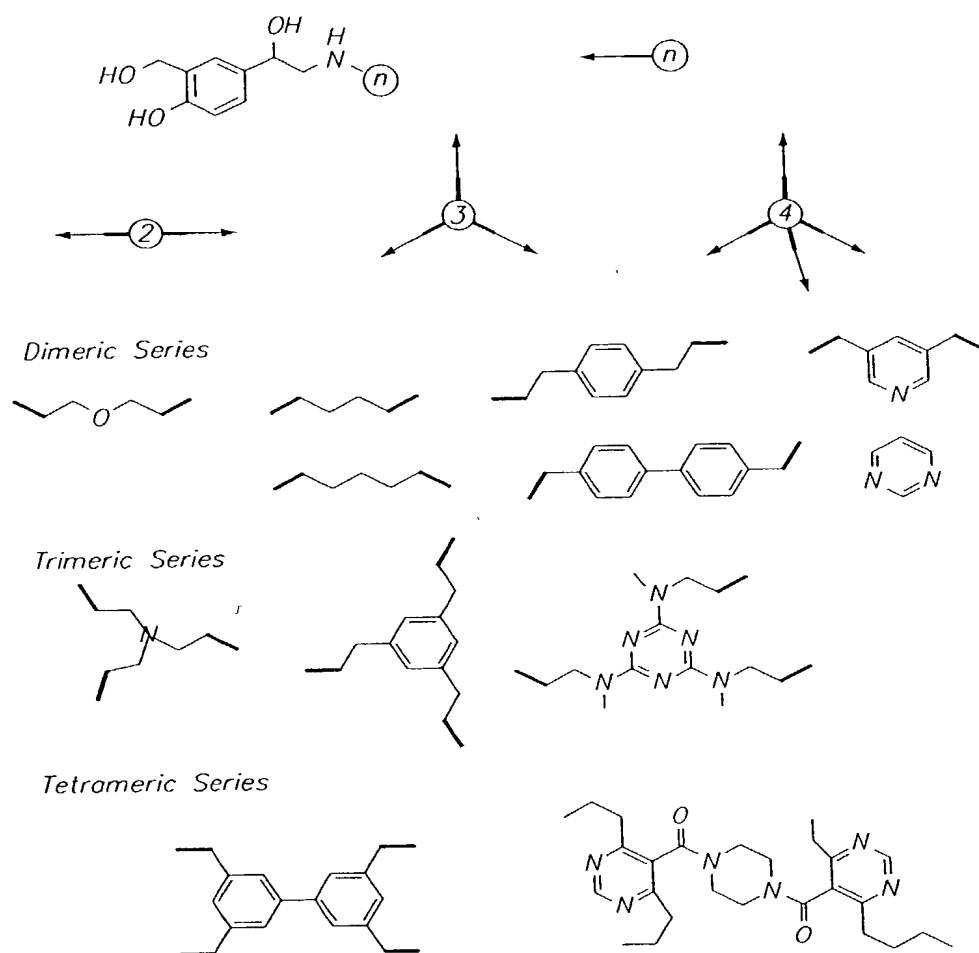
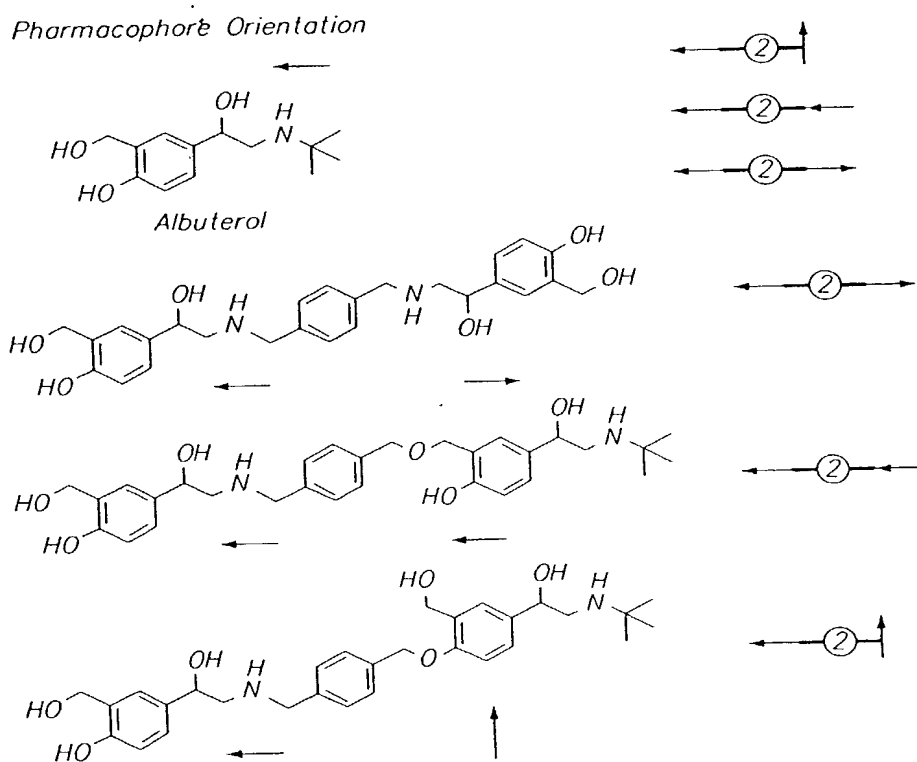


FIG. 52

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Albuterol Multivalomers 4-Relative Pharmacophore Orientation



Albuterol Multivalomers 5-Mixed β_2 Adrenergic Heterovalomers

Heterovalomers

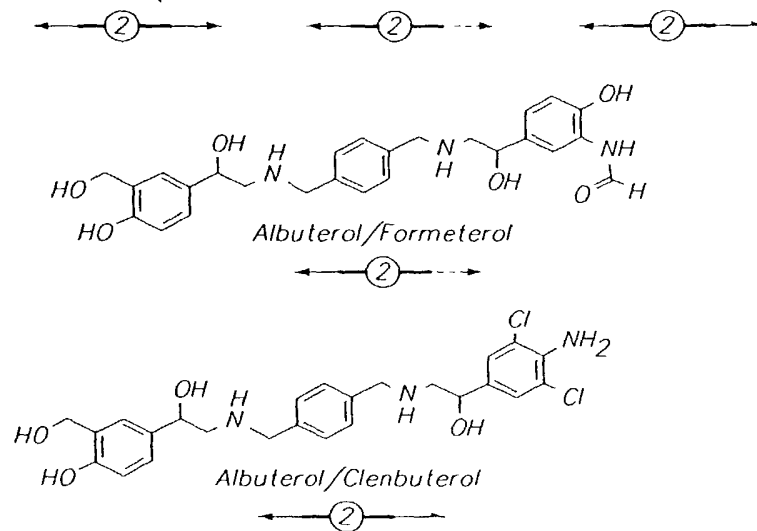
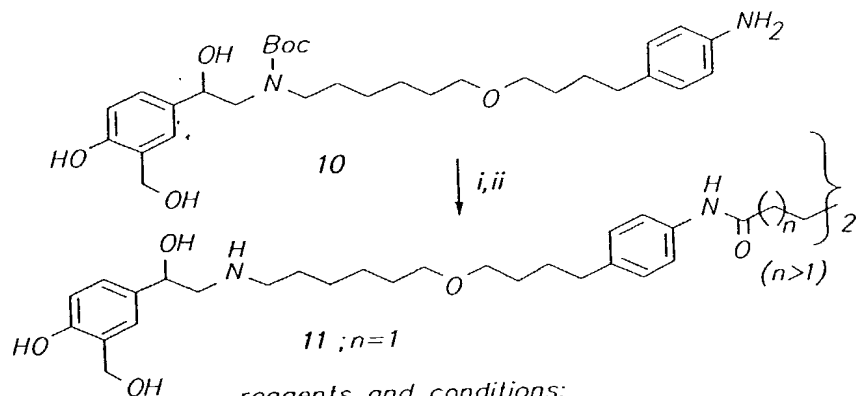


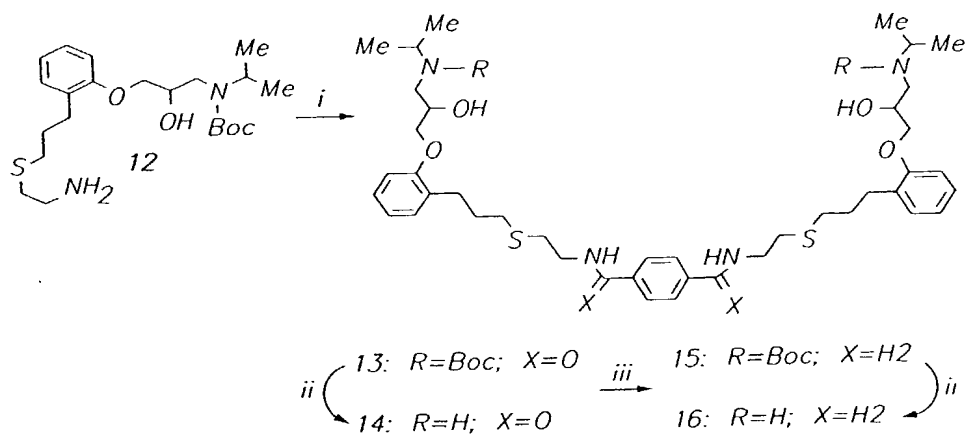
FIG. 54

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reagents and conditions:
i) 1,6-hexanedioic acid, DIPEA, HOBT, PyBOP, DMF, rt.
ii) TFA/CH₂Cl₂, 0°C.

FIG. 57



reagents and conditions:
i) terephthalic acid, DIPEA,
HOBT, PyBOP, DMF, rt;
ii) TFA/CH₂Cl₂, 0°C;
iii) LiAlH₄, THF, 80°C;

FIG. 58